Acta Genetica et Statistica Medica

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Vol. V 1954 No. 1

INDEX

BASEL (Switzerland) S. KARGER NEW YORK

Printed in Switzerland

"*Acta Genetica et Statistica Medica*" is issued quarterly. Each issue has approximately 96 pages. The annual subscription rate is Swiss frs. 48.—.

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«*Acta Genetica et Statistica Medica*» paraît en fascicules trimestriels d'environ 96 pages. Le prix de l'abonnement annuel est de frs. suisses 48.—.

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«*Acta Genetica et Statistica Medica*» erscheint vierteljährlich in Heften von etwa 96 Seiten zum Jahresabonnementspreis von sFr. 48.—.

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THE BASIC CONCEPT OF RACE

By GUNNAR DAHLBERG, Uppsala

1. First, from a theoretical point of view, a race is an isolate or a group of isolates for which the frequencies of specific genes are more or less different as compared with other groups of isolates. This definition is quite clear and is used mainly by geneticists. It will probably be more widely accepted in the future.

2. Our knowledge of the genes and their different frequencies, however, in different groups of people is not yet sufficient for the above definition to be generally applied for practical purposes. For human beings a less clear definition of hereditary differences between groups has been used. Definite statements can be made about very few definite characters only (viz. blood groups). Physical anthropology arose long before mendelism. Although anthropology is based on the analysis and comparison of characters which largely depend upon genetic factors, anthropologists have not quite incorporated the genetic viewpoint. We are informed mainly about relatively trivial morphologic differences in a descriptive way.

An example of the difficulties following this vague conception will be given. *Retzius* and *Fürst*, in their well-known work Anthropologica Suecica [1902] assumed that the Nordic race had the following characteristics: a stature of 170 cm., a cephalic index below 75 per cent, blond hair and gray or blue eyes. They found that 10.07 per cent of the Swedish population had these traits and consequently were of Nordic race (der reine ungemischte germanische Typus). This postulate can be tested on a single character, viz. stature. According to the investigations by *Hultkrantz* [1927] the average stature of Swedish conscripts is known from the year 1840 up to the present time. Stature increased by 9 mm. per decade from the year 1840 to 1923, i.e. 9 cm. in a century. Supposing that other characteristics have remained unchanged, in 1840 only about 3.8 per cent fulfilled the conditions stipulated by *Retzius* and *Fürst*. The change cannot be due to mixture with foreign elements. It could be due to a better environment (better food). For several reasons this possibility is not very likely. Another possibility is that because of the breaking up of isolates (better communications, industrialization and increased urbanisation) the gene combinations have been altered. Anyhow, the example shows the necessity of taking genetics into account.

With respect to psychic differences there is a tendency to utilize traits due to dissimilar cultural patterns. Modern sociology and anthropology have widened our knowledge of these different cultural patterns considerably and have led us to associate the race concept with such differences as we know are products of the cultural pattern and therefore most likely, but by no means certainly, are of environmental origin. Consequently sociologists and anthropologists often disagree about the race concept. Our knowledge is yet too scanty to permit anything but hypotheses, however. It is equally wrong to deny the existence of races on general principles as it is to maintain that some psychic differences are racial and therefore hereditary. The race concept is and will for a long time remain a way of qualifying dissimilarities about which we know very little.

3. In popular discussions a pre-mendelian concept of race is often used. This concept is based on the theory that the material basis of inheritance is a homogeneous material which can be diluted and mixed as we can mix whisky and soda. Accordingly one speaks of half-pure blood or half-breed and so on. Every race is assumed to have a hereditary substance of its own different from that of other races. Different individuals belonging to the same race could have different characteristics, as different objects may be made of copper or of tin. Between different groups, however, there was supposed to be a real difference in regard to the basic material. This popular concept is of course quite incorrect.

This erroneous idea is seldom exposed but may be maintained unconsciously. It might be added that a common misuse of the term race appears in politics and in patriotic speeches. When applied to one's fellow citizens the term "race" is used in a flattering sense. This is the case if the patriotism is rather mild and one wishes to say only that some special "race" characters are of special value for humanity. Even cautious expressions often lead people to think that their own race is especially valuable as compared with other races. It is necessary for every person to feel that he or she is in some way important and perhaps this is necessary for a people too. Anyhow, it is not only incorrect but gravely misleading to mix patriotism with the concept of race which in this connection is especially dubious. This applies still more to the reverse situation when discussing people or groups who are looked upon as enemies, potential enemies or competitors. Needless to say, one has thereby left the scientific approach to race problems and jumped into assessment of values.

Böök, J. A.: Acta genet. 5, 3–12, 1954

RACE MIXTURE[1]

By J. A. BÖÖK, Uppsala

To most people the concept of race or race mixture has a more or less strong emotional connotation. Most people are also inclined to consider the group to which they belong as particularly outstanding from a cultural or some other special point of view. It is only natural that through such assessments of value, which sometimes are made subconsciously, the possibility of judging these problems rationally is lost. In addition, most of the traits usually emphasized as characteristic of a racial group lack either biologic significance or objective meaning.

In common, and unfortunately very often also in scientific language, the word «race» is used with a number of different meanings. To be able to discuss race mixture it is therefore necessary to explain the modern concept of race in terms of population genetics.

To understand a number of common misunderstandings it should also be remembered that modern genetics dates back only to the year 1900, and that the influence of genetics on physical anthropology is a quite recent feature. Previously it had been the common understanding that inheritance depended on parental propensities mixed in such a way that the offspring was regarded as some kind of an alloy. Such concepts as "half-blood" and "quarteron" are linguistic relics from this period. *Charles Darwin* also understood the mechanism of inheritance in this way but fortunately did not develop further the consequences of this theory in connection with his own theory of evolution. If inheritance meant a blending, it would follow that genetic variation would decrease fifty per cent per generation. This would imply that any population in a short time would become genetically homogeneous. Selection would be without any effect as far as the offspring was concerned, and further evolution according to *Darwin*'s theory would be impossible.

[1] Lecture given at the University of Uppsala, May 14th, 1954.

The idea of pure races is also based on this superceded concept of the mechanism of inheritance. As mentioned above, it was not until quite recently that the classic, more descriptive physical anthropology started to use a more dynamic approach in which genetics takes an essential part. The lack of any more scientific approach made it possible to distribute all kinds of nonsense about race and race mixture under the pretence of science as pointed out by *Dahlberg* [1942]. There are numerous examples which could be cited to demonstrate how the concept of race has been utilized for nationalistic, imperialistic and a number of other political purposes and mostly with disastrous consequences.

Therefore, some anthropologists and geneticists regard the very word "race" so disqualified that it should not be used. One suggestion is to talk about ethnic groups. However, this hardly seems to be a rational solution as the race concept is already well established in such biologic sciences as zoology and botany.

When discussing races and race mixture, it is not sufficient to consider only a cross section of the world population at a given moment. It is also important to consider the evolution of human populations. Up to about the middle of the 15th century the population of the earth consisted of relatively strongly isolated groups. There had, of course, been transmigrations of people, conquests and settlements in new localities, but in comparison with later developments these early migrations were rather insignificant and, above all, they did not imply new contacts between people with quite different characteristics.

Early geographic isolation, prevalent for many thousands of years, caused a differentiation between population groups. Each of these groups reached a certain degree of adaptation to their special environment. This process was explained by *Darwin* as coming about through selection. The adequate explanation of the mechanism of evolution, however, was not produced until *Mendel*'s discoveries became known and appreciated. The most fundamental concept in *Mendel*'s discovery is the fact that inheritance is particular. Sexual propagation, therefore, does not mean a blending but a recombination of the particles of heredity, i.e. the genes. Sexual propagation does not destroy but conserves the genetic variation. Therefore, selection can —just as *Darwin* thought—cause changes in the genetic structure of a population *via* environmental influences on genetically determined traits.

The key to the modern race concept lies in this evolutionary and dynamic view. Races are populations which, mainly because of geographic isolation, share a common gene pool. Naturally, the geographic isolation between the populations of the earth has never been complete. There have always been borders where mixtures and gene exchanges have occurred. Therefore, the differences between neighbouring populations are always smaller than between those far apart. How great a difference should be to be called a race difference is more or less a matter of statistic consideration. Difficulties in distinguishing between races are an unavoidable consequence of the proceeding evolution.

Insofar as geographically widely separated populations are concerned, selection and adaptation have caused such pronounced genetic and phenotypic differences that the distinction of separate races does not raise any difficulties. In this discussion of race mixture it is primarily crossings between individuals of just such widely separated populations which will be considered. Generally one does not talk about race mixture when neighbouring populations are concerned.

Due to the earlier very restricted individual mobility there were no real problems of race mixture until the middle of the 15th century, at any rate, not of the magnitude that has occurred later. A quite new era began when the great exploring expeditions took people, above all the Europeans, to remote countries and continents. Thus a basis was created for race mixtures of the tremendous proportions that are so typical of our time.

To give some idea of the magnitude of population movements during the last five hundred years it could be mentioned that about 3 million Spaniards migrated to South America from 1450 to 1600. From 1820 to 1935 about 35 millions—mainly Europeans—migrated to the American continent. From the beginning of the 16th century to about 1850 at least 15 millions Negroes—mainly West Africans—were transferred to North and South America. Well known is also the expansion of the Asiatic population, especially the Chinese and the Japanese, to the islands of the Pacific and to the USA.

All these migrations together with the European colonization immediately caused race mixture on a large scale. Thus the foundations of large mixed populations were laid down in many parts of the world. It is not possible to give a satisfactory estimate of how many individuals of mixed origin there are in the world today. However, it is justifiable to venture a guess of close to 50 million. This figure is

probably on the minimum side. Race mixture, therefore, is a problem that certainly has more than academic interest.

Social aspects.

It is, in fact, the social consequences of mixed marriages that have made race mixture a problem of modern times. If race mixture had been accepted as a natural phenomenon everywhere, the offspring of such marriages would eventually be assimilated in the population, which thereby, of course, would undergo a certain biologic change. Such a process is no doubt going on in all populations in which there is race mixture, but it occurs with quite a different speed in different countries. The social resistance to mixed marriages may vary a great deal. In certain countries, e.g., Paraguay and Mexico, race mixture has been accepted without any restrictions. In most other places, however, the resistance has been very hard. The reasons are very complex, and it will only be possible to mention a few main points.

Race consciousness and nationalism are more or less characteristic for all peoples. In this there are always such components as ideas of superiority to other peoples. Such ideas have always reached larger dimensions the more physically and culturally different these other peoples have been. Peoples with a more advanced technical culture have always tended to consider techniques as the only important criterion. Technical underdevelopment has been interpreted as a symptom of cultural backwardness in general.

These ideas bring us over the role played by imperialism and colonization in race discrimination. The myth of the superiority of the White man or the White race was invented to further colonization enterprises and to serve political and economical purposes. For a few Whites in a colony it was necessary to create a wall between the ruling and the ruled class. Race mixture would only create complications which could be disastrous for the existence of the White race. In countries of a less pronounced colonial character, e.g., the USA or South Africa, this sharp distinction could not always be upheld.

Instead, a typical cast society developed. Race mixture took considerable proportions, but the offspring of this mixture met social difficulties and were expelled to the group which according to the opinion of the Whites was the lower one, i.e. the coloured population. In other instances, e.g., race mixture between Chinese and Europeans, the offspring found themselves expelled from both parental groups and were forced to create a cast of their own.

It is only too evident that behind this social discrimination against race mixture lies nothing but egotism, ignorance and superstition.

Biologic aspects.

Among the biologic arguments which are currently raised against race mixture, the most common ones are founded on ignorance of the evolution of man. A common misunderstanding is that the different human races could be arranged according to their degree of evolution as originating from a common primitive stock. So-called primitive races are considered to entertain a lower cultural level, which is supposed to depend on inferior intelligence and inferior moral qualifications. Finally, many seem to accept flatly the idea that such mental traits are to a very high degree genetically determined. Consequently, it is said, race mixture produces offspring who, from the point of view of the more advanced race, represent a step backwards. Similar ideas lie behind the hypothesis that race mixture inevitably leads to degeneration.

In fact, however, all reliable data we have concerning man's evolution indicate that the differentiation of races has taken place rather simultaneously. In comparison with the anthropoid apes, all human races display a very pronounced differentiation. As *Shapiro* [1953] points out, the advocators of the higher degree of development of the White race should perhaps hesitate to use the above-mentioned arguments of evolutionary differences considering, e.g., that the thick lips and the frizzy hair of the Negroes are more "evolved" from the simian level than the corresponding traits of the White race. Every race has been adapted to its environment, and the history of human evolution as we know it does not support any attempt at a hierarchic subdivision of human races now living. The argument concerning mental differences, when scrutinized, appears more cultural than biologic. Regardless of the fact that statements concerning racial mental superiority sometimes have been based on the results of psychometric tests, the way in which the genetics of mental traits are treated is so careless that the statements must be rejected. Today most geneticists and psychologists agree that psychometric tests on the whole measure phenotypic intelligence, although there is undoubtedly a significant genetic component. So far the available tests can give some information about the genetic variation within a certain population, but they cannot be used for purposes of comparing populations with a quite different cultural background. Consequently,

we have no proof that there are any important differences in regard to genetic intelligence between different human races. Although there are as yet no proofs, it is quite conceivable that some mental differences do have a significant genetic background. The problem is, therefore, not one to be dismissed.

Besides the fact that evaluations which ascribe superiority to certain races are unscientific and disgraceful, available biologic and evolutionary facts leave no reason for keeping any discrimination between races or race mixtures. All scientists agree that all the human races now living belong to the same species. The differences between races represent differentiations and adaptations of each race to its special environment. Genetically, the races are populations with partly dissimilar gene pools. The genetic differences, however, do not seem to concern fundamental human traits but rather adaptive variations. Race mixture, therefore, can be expected to give offspring who display either maladaptation to the parental environment or a better adaptation. As always in a crossing between individuals who are different in regard to a large number of genes, the first generation will be intermediary, and subsequent generations will display a very considerable variation. Race crossings, therefore, tend to increase the genetic variation and thus provide extra raw material for selection and evolution. It should also be pointed out that in all natural populations of plants or animals selection seems to favour heterozygotes. A number of recent investigations seem to show that, in general, heterozygotes display a better viability (i.e. heterosis). This is probably a general phenomenon which is also valid for man. A more pronounced and new type of heterozygosity can be expected to result from race crossing. It is to be anticipated that this, at least sometimes, would imply adaptively advantageous results. In an investigation of about 300 descendants of Hottentots and Dutch or German farmers *Fischer* [1913] found an increased height in comparison with both parental groups. The general viability in this mixed population was judged as excellent. Mortality was low and the fertility with an average of 7.7 children per marriage was at any rate higher than for the White parental group. It seems probable that these results to some extent were due to a heterosis effect.

Investigations of race crossings.

Considering the importance of race crossing from a social and political point of view, it is surprising how very few actual investi-

gations we have in this field. The available investigations which are unbiased as well as scientifically acceptable certainly do not support any of the quasi-scientific writings, a great number of which has been offered to the public, and which more or less openly defend discrimination and superseded views. *Fischer*'s above-mentioned study did not disclose any signs of degeneration or disadvantages. In general, most differences in comparison with the parental groups could easily be explained as due to different environment or a different culture.

The story of Pitcairn (cf. *Shapiro* [1936]) gives another example of race crossing without any resulting disadvantage. After the mutiny on the Bounty this island of Polynesia was colonized in 1790 by some dozen English sailors, Tahitian men and women. The population originating from these people now amounts to some 1,000 individuals, of whom only about half live on the original island. As an example of race mixture this population is quite unique because, due to a very long complete isolation, it has been free from all the different kinds of taboos which otherwise make life quite complicated for mixed groups. Nobody who has examined or contacted this population has been able to find any signs of disadvantageous effects of race mixture. On the contrary, these people display a very fine adaptation to their environment and, in spite of the isolation, they developed a high cultural standard with some original components.

The only actual investigation commonly cited by the opponents of race mixture is *Davenport*'s work of 1929, "Race Crossing in Jamaica". By and large, this is a report of race differences between Whites and West Africans and of the quality of the offspring of such mixed marriages. The offspring, or the Mulattoes, are claimed to be physically as well as mentally inferior to both parental groups. *Davenport* was of the opinion that this was mainly due to disharmonic gene combinations. This work was recently scrutinized and criticized by *Shapiro* [1953], who seriously questioned or rejected most of *Davenport*'s statements. *Shapiro* has shown that the data do not meet reasonable requirements of representativity. Sweeping generalisations have repeatedly been based on scanty observations. When the comparisons of the psychometric test scores of the offspring and the parental groups have been corrected, there remains the result that the Mulattoes do not deviate appreciably from the Negro population but score less than the Whites. This is in agreement with findings in the USA. However, it must be remembered that Mulattoes and

Negroes belong to the same social stratum. Therefore, it is probable that differences in environment are most important. No less important is the fact that there have been repeated re-mixtures between Mulattoes and Negroes but not—or very insignificantly—with the Whites. Biologically the Mulatto population was, in other words, not intermediary but closer to the original Negro population. Furthermore, one should not ascribe too much importance to means. The variability within groups was considerably greater than that between them.

Summing up our present knowledge of race crossings, i.e. knowledge backed up by facts, I think the correct conclusion would be that no proofs have been produced to the effect that such crossings are necessarily disadvantageous from a biologic point of view.

Some of the difficulties of race research are due to the fact that the relation of most classical anthropologic traits as hair, skin and eye colour, stature and all different kinds of somatic indices to their genetic background is not sufficiently known. Many such characteristics appear genetically too complex to serve other than purely descriptive purposes. Therefore, new pathways have been explored and especially the blood group research has exerted a great influence on physical anthropology during the last few years. In many cases it has been possible to demonstrate marked differences of gene frequences of different blood group alleles. Recently *Glass* [1953] has suggested a method to calculate by means of such allele frequences the magnitude of race crossings and the speed by which a nation in which race crossings occur is transferred into a more homogeneous population. The method is certainly rather crude and based on premises some of which are rather dubious, but on the whole it should give a good estimate of some features of race dynamics. As an example it could be mentioned that the blood group Rh_0 (cDe) has a frequency of 2–3 per cent among US Whites. Among US Negroes the frequency is 45 per cent and for Negroes from West Africa 65 per cent. The intermediary frequency for US Negroes agrees rather well with what could be expected after the race mixture that has occurred in the US since 1650. *Glass* calculated that the Negro population in the US has probably received about 30 per cent of its gene pool from the Whites through race mixture. The movement in the opposite direction has been rather insignificant. As this process proceeds, for every generation an increasing number of "Negroes" will pass the colour line and disappear into the White population, until finally the Negro in the

USA virtually disappears. It was estimated that this process would take some one thousand years.

In retrospect of everything said and written about races and race mixture I think one is justified to state that much of it, perhaps the most, represents desk speculations or pure superstition. Modern genetics and biology has shown that human variation whether within or between populations or races, has to be accepted as a fact due to the forces of human evolution. Crossings over the usual borders is a consequence of technical developments and world-wide social progress. It has also to be accepted that there is no reason to consider race mixture as a price to pay for these developments, as no harmful biologic effects resulting from it have been demonstrated. The harmful effects of race crossings and the problem itself is *not* created by nature but by man and it can only be removed by man.

Summary.

A short survey of the social and biologic implications of race crossing in man. There are few actual investigations on the effect of race mixture which can be considered to meet the requirements of objectivity and freedom of methodologic biases. Acceptable data do not justify the conclusion that, from a biologic viewpoint, race mixture is disadvantageous or undesirable. The race problem appears very much to be a man-made problem, created by personal idiosyncrasies and political biases.

Résumé.

L'auteur donne un aperçu de ce qu'implique chez l'homme d'un point de vue social et biologique le croisement de races différentes. Il y a peu d'investigations faites actuellement sur l'effet d'un croisement de races qu'on puisse considérer comme satisfaisant les exigences de l'objectivité et l'absence d'idées préconçues. Des données plausibles ne permettent pas de conclure que le croisement de races serait défavorable ou indésirable d'un point de vue biologique. Il semble que le problème de races soit en grande partie un problème créé par les hommes par suite d'idiosyncrasies personnelles et de préjugés politiques.

Zusammenfassung.

Eine kurze Übersicht der sozialen und biologischen Folgen der Rassenkreuzung beim Menschen. Zurzeit gibt es nur wenige Unter-

suchungen über die Wirkungen der Rassenmischung, welche den Forderungen der Objektivität und des Freiseins von systematischen Vorurteilen Genüge leisten. Anerkannte Ergebnisse rechtfertigen nicht den Schlußsatz, daß Rassenmischung von einem biologischen Gesichtspunkt aus schädlich oder nicht wünschenswert wäre. Das Rassenproblem scheint in hohem Maße ein menschliches Erzeugnis zu sein, hervorgerufen durch persönliche Idiosynkrasien und politische Vorurteile.

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Lancaster, H. O.: Acta genet. *5*, 12–24, 1954

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THE EPIDEMIOLOGY OF DEAFNESS DUE TO MATERNAL RUBELLA

By H. O. LANCASTER

1. Introductory.

A general review of maternal rubella as a cause of congenital anomalies has been given by *Aycock* and *Ingalls* [1946]. It is proposed to give here a more limited account of the incidence of congenital deafness throughout the world with the aid of census and institutional data, in order to stress the importance of isolation in producing large proportions of susceptible adult females. The experiences of Australia, New Zealand and Iceland are contrasted with those of Italy, Sweden, England and the United States.

2. Census Data.

At the meeting of the International Statistical Institute held at St. Petersburg, Russia, in 1872, it was agreed that the census form should include a question on infirmities and that special mention should be made of blindness and deaf-mutism. A number of countries have included such a question, largely to determine the number of children likely to require special schooling or to ascertain the employment of the deaf. It appears that little of epidemiological importance has come out of the answers to this question in any country other than Australia. Only in the Australian figures could one have good reason for suspecting epidemicity of the causes of deafness from them.

(i) *Australia.* The data for Australia, collected at the Censuses of 1911, 1921 and 1933 have been reviewed (*Lancaster* [1951b]). It is evident that after the report of *Knibbs* [1917] it would have been possible by following this lead to incriminate an epidemic disease occurring in pre-natal life, since any cause acting post-natally could not very well have given such a sharp epidemic wave to the births.

(ii) *New Zealand.* The census reports for the Census of 15th October, 1916, for New Zealand show no evidence of epidemic increase for any age-group. The rates per million at ages 15 to 19 years, are 178 for males and 151 for females, which are both lower than the rates at ages 20 to 24 years, 394 and 214. It is clear that no one would be led to suspect epidemicity by reading the table of incidence of deaf-mutism by age. In fact, the rates are lower in the age group containing those born in 1899, an epidemic year for births (*Lancaster* and *Pickering* [1952]), than they are in the next older age group.

(iii) *England and Wales.* In the census of England and Wales in 1891, deaf-mutes were enumerated by age, sex and county. Some irregularities are to be noted but they are probably due to irrelevant causes since the irregularities are not apparent in the 1901 Census.

(iv) *Canada.* Questions on deaf-mutism were asked in the censuses of 1891, 1921 and 1941. In 1891 and 1921, the age grouping was not sufficiently fine for our purpose. In the 1941 Census, the age distribution is five-yearly and by provinces. No evidence of epidemics can be found.

(v) *The United States of America.* At some American censuses a question has been asked on deafness or deaf-mutism. In particular,

after the census of 1900, a detailed analysis was made of the deafness statistics (U.S. Bureau of Census, 1906). *Alexander Graham Bell* has written the commentary on the information collected. A circular letter was sent to each person (or his guardian) who had been entered in the census returns as deaf or deaf and dumb. The special schools for the deaf were also required to furnish returns. From Tables VI, LX and LXI of the report, there is no suggestion of epidemicity. It may be argued that epidemics if not occurring throughout the States in one year might leave no mark on the official statistics. So that a more detailed analysis of institutional data might be informative.

(vi) *Iceland.* At the census of December 1940, 112 persons were recorded as deaf-mutes but no conclusions as to epidemicity can be drawn.

(vii) *Other Countries. J. Koren* [1904] reviewed the census reports for Germany on deafness. It seems that other diseases such as cretinism have caused high incidences of deaf-mutes in some areas making it difficult to detect epidemicity due to less frequent causes. At the same time the deafness was higher in the north-eastern areas of Germany where cretinism is less common. It seems that a search may yield areas where the epidemiology of rubella resembles the Australian and so where epidemic deafness can occur. Other factors such as inbreeding have to be considered in comparing different areas in Europe.

3. Institutional Data.

(i) and (ii) *Australia and New Zealand.* The data available from the chief institutions for the deaf have been collected and analysed previously (*Lancaster* [1951b], *Lancaster* and *Pickering* [1952]). It is unnecessary to repeat the discussion here. A case of maternal rubella deafness born in 1924 had been reported by *Gregg* [1945].

(iii) *Iceland.* It seemed likely that Iceland might have an experience of the Australian type because of its isolation. I have been able to secure data on the incidence of both deafness and rubella (*Jónsson* [1951] personal communication); they are included in Table I which summarizes the births of those attending the institution for the deaf in 1951.

It is evident that two or less births of the deaf per year might be considered normal for Iceland. But one year, 1941, is quite exceptional as in that year ten children were born, later to be reported as deaf. Moreover, there is a distinct bunching up of the births by months, one

Table I. The births of the deaf in Iceland (Preliminary Report by Dr. *V. Jónsson*, Landleaknir, Reykjavik, Iceland).

Year	Births of the Deaf later in Institution	Month of Birth	Notifications of Rubella
1935	2	7 and 11	9
6	1	6	9
7	0	–	32
8	1	6	55
9	2	6 and 6	8
40	2	3 and 4	781
1	10	1, 5, 6, 6, 7, 8, 9, 9, 9 and 9	1566
2	2	7 and 10	29
3	1	4	94
4	1	1	34
5	1	10	12
6	0	–	16
7	1	4	357

Total population of Iceland, in 1940, 121,474. Births about 2,500 per annum.

being born in May, two in June, one each in July and August and then four in September. This adds weight to the suggestion that there was some epidemic cause acting. In Iceland, rubella is a notifiable disease and in 1940 there were reported 781 cases and in 1941, 1566. This suggests that the epidemic cause may be rubella. (It is understood that an investigation is being carried out in Iceland on the aetiology of these cases of deafness.)

(iv) *England and Wales.* Through the courtesy of Mr. *F. W. Cockersole* (personal communication [1952]) and Mr. *J. Spalding* (personal communication [1952]), I have been able to obtain the births of the deaf educated at the Royal School for Deaf Children, Birmingham, and the Royal Residential School for the Deaf, Manchester. The experience of these two schools may be taken to be representative of England and Wales. The births are given by years for the two schools combined in Table II.

It is seen that no dramatic epidemic episodes have occurred. But a dissection of the births by month and year reveals some suggestive figures. Thus at Birmingham there were 9 births in September and 12 in October, 1940, whereas the monthly average is less than 2.5 for the preceding ten years. The only other suggestive months were March and April 1893 with 8 and 5 births respectively. Manchester with 6, 8, 4 and 6 births for the last months of 1940 has also

Table II. The Births of the Deaf in England[1].

Year[2]	0	1	2	3	4	5	6	7	8	9
189—	53	45	65	54	45	53	72	78	73	68
190—	65	80	69	63	73	89	77	74	67	59
191—	58	72	59	54	62	51	56	51	49	67
192—	63	81	48	52	57	42	70	43	52	49
193—	55	57	50	57	54	55	68	48	72	71
194—	94	62	39	49	57	42	49	36	20	5

[1] The Births of Children later to be admitted to the Royal Residential Schools for the Deaf, Manchester, and Royal School for Deaf Children, Edgbaston, Birmingham.

[2] For printing convenience, the years have been grouped into decennia. The first three digits of the year are to be read from the left hand margin, the final from the column heading.

a suggestive period. At Manchester the births for 1893 are not suggestive of an epidemic. *Clayton-Jones* [1947] has given evidence that some of the pupils at these schools who were born in 1940 were deaf as the result of maternal rubella.

(v) *Scotland.* I have been unable to obtain institutional data from Scotland other than that published in the report of *Grant Keddie* [1945]. Inspection of the number of births of the deaf for the years, 1908 to 1936 does not reveal any evidence of epidemicity.

(vi) *Italy*. As representative of Italian experience I have been fortunate in securing, through the courtesy of Dr. *A. Gaddi*, the date of births of all children later to be admitted to the state institution for the deaf in Rome (*Gaddi*, personal communication [1952]). The frequency of births by year is shown in Table 3. The low numbers of births of the deaf in Italy over the later years of the First World War are to be explained by a low general birth-rate there at that time. There is no evidence of epidemicity, that is, the number of births in any year can readily be explained by random fluctuations due to chance factors.

(vii) *Sweden*. From Sweden, by the courtesy of Mr. *N. Malm* (personal communication [1951]), I have secured the date of birth of every child later to be admitted to one of the Central Schools for the Deaf-and-Dumb at Manilla, Sweden. A summary is given in Table IV. It is evident that no epidemic episodes can be detected with any certainty before 1936. In that year there were 22 births and in 1937, 23, which although suggestive might well have been passed over as it is towards the end of the experience and, moreover, the births do not show any marked grouping by month. However,

Table III. The Births of the Deaf in Italy[1].

Year[2]	0	1	2	3	4	5	6	7	8	9
187—	–	–	–	–	–	14	13	16	9	25
188—	21	28	32	22	28	22	23	15	26	25
189—	23	15	16	22	24	17	20	16	13	13
190—	11	22	26	24	23	17	14	10	20	12
191—	15	22	21	19	23	22	18	3	8	12
192—	19	16	11	12	16	16	13	19	20	13
193—	24	14	17	20	24	25	18	23	25	25
194—	33	15	25	15	26	10	8	1	–	–

[1] From data supplied by the Director, Instituto Statale dei Sordomuti in Roma.
[2] See Table II for method of expressing the year.

Ivstam [1951] has noted that in Sweden there were 3 births in 1936 and 11 births in 1937 of children later to be admitted to Swedish schools for the deaf, deaf from maternal rubella.

Table IV. The Births of the Deaf in Sweden[1].

Year[2]	0	1	2	3	4	5	6	7	8	9
190—	10	12	13	10	14	11	12	11	15	14
191—	20	14	11	13	11	15	15	12	15	20
192—	12	13	19	8	19	14	15	16	14	8
193—	5	12	10	6	10	9	22	23	13	9
194—	14	18								

[1] From data supplied by the Director of the Manilla Central School for the Deaf-and-Dumb, Stockholm.
[2] See Table II for method of expressing the year.

(viii) *The United States of America.* In the latter part of the nineteenth century there was a great deal of interest in problems of deafness and mutism. *A. G. Bell* [1884] put forward the hypothesis that the deaf by intermarriage were producing a deaf variety of the human race. *Fay* [1898] undertook to examine the records of the marriages of all deaf persons in the United States and Canada. He believed that the majority of the marriages of the deaf contracted in the United States and Canada had been included in his survey. The date of birth of each deaf person is given. The deaf may be divided into two series according as to whether they have not or have deaf siblings. I have termed these series, A and B, in Table V. Series A of the deaf with no affected sibling might be expected to include the majority of those deaf due to non-genetic causes. From the date of

Table V. The Births of the Deaf by years in the United States of America.

Series[2]		Year[1]									
		0	1	2	3	4	5	6	7	8	9
180—	A	2	2	3	3	5	7	13	17	18	20
	B	1	1	2	6	3	13	9	5	5	5
181—	A	19	21	25	32	27	33	19	17	15	21
	B	7	10	4	6	11	17	11	7	12	13
182—	A	23	31	25	22	32	39	19	49	34	32
	B	13	20	24	23	20	14	27	17	20	27
183—	A	34	35	44	44	35	31	55	53	72	59
	B	12	25	22	29	24	21	37	20	34	23
184—	A	67	75	65	76	76	83	82	77	77	87
	B	39	30	27	33	33	50	51	46	37	46
185—	A	87	92	102	104	103	100	128	123	163	171
	B	46	42	46	47	47	38	56	42	44	65
186—	A	179	168	186	174	153	151	120	94	100	95
	B	53	56	50	51	40	40	36	31	25	41
187—	A	78	40	26	17	11	1	6	–	–	–
	B	14	12	8	11	2	1	1	1	–	1

[1] See Table II for method of expressing the year.

[2] Two (2) series have been analysed. A includes births of those deaf who have no sibling also affected, B includes those with an affected sibling, both series from *Fay* [1898].

collection, one can expect that there will be little information on births after 1870. There is no evidence of epidemicity to be noted in Table IV in either series A or B.

In Table VI is given the number of births each year of children later to be admitted to the Central Institute for the Deaf, St. Louis, Mo., U.S.A. (*Silverman*, personal communication, 1952) and to the Clarke School for the Deaf, Northampton, Mass., U.S.A. (*Hopkins* personal communication [1953]). In the data of these two institutions there is some evidence suggestive of epidemicity. At St. Louis, 1918 with 25 births and 1943 with 23 births are the most suggestive years. August and September 1918 have four births each which may be regarded as possible evidence for a small epidemic. In November and December, 1943, there were 5 and 4 births respectively and this again is suggestive. This evidence is greatly strengthened by noting that there were four, five and four births in Northampton, Mass., in August, September and October, 1918. The monthly incidence of some of the more suggestive periods at Northampton, Mass. is detailed in Table VII. It appears that there were minor epidemics approximately centred on December, 1871; on December, 1881; on

Table VI. Births of the Deaf by Years in two Institutions in the United States of America.

Year	0	1	2	3	4	5	6	7	8	9
Central Institute for the Deaf, St. Louis, Mo.										
189—	–	–	–	–	–	–	–	1	2	3
190—	2	5	1	6	3	5	4	8	13	3
191—	16	13	13	14	14	11	10	18	25	11
192—	15	4	13	18	12	21	21	23	15	7
193—	18	7	10	9	6	16	10	5	7	12
194—	12	14	15	23	6	8	12	6	5	–
The Clarke School for the Deaf, Northampton, Mass.										
184—	–	–	–	–	–	–	1	0	2	0
185—	1	3	1	5	3	2	5	5	14	6
186—	9	11	9	11	10	7	8	11	13	11
187—	14	27	17	13	17	11	14	16	13	17
188—	21	24	24	14	12	25	15	20	21	22
189—	18	26	10	27	23	22	24	16	29	14
190—	19	20	24	24	19	28	32	19	17	23
191—	19	16	21	31	31	26	22	27	37	24
192—	26	21	19	15	14	18	18	21	24	19
193—	13	19	21	20	19	21	14	7	9	10
194—	13	12	16	18	11	7	17	11	4	

April, 1898; on February, 1902; on December, 1905; on December, 1913; on December of each of the years 1917, 1918 and 1919; on December, 1935 and on December, 1943. It seems that these Massachusetts data suggest that deafness has been occurring as an endemic disease without any dramatic outbursts in Massachusetts over the last eighty years, at any rate. Miss *Hopkins* (personal communication) notes that all parents of pupils graduating in the last ten years have been asked for details of infective disease in pregnancy and as a result the 1935–36 and 1943–44 epidemics had been revealed, as also single cases in 1927 and 1928 and two cases in 1942. Details are given in *Hopkins* [1946].

A neglected factor, which may have been of some importance in the Australasian epidemics, is birth order. Thus *Hay* [1949] found that of 100 rubella positive cases of congenital defects, 49 were first born and 25 second born children. This is rather surprising as the mothers of school children might be expected to have a higher risk of infection, as they have in other childhood diseases, such as scarlatina (*Pope* [1926]). It seems quite likely that an aggravating factor in the

Table VII. Periods Suggestive of Epidemicity of the Births of the Pupils of the Clarke School for the Deaf, Northampton, Mass., U.S.A.

Year	The Number of Births of the Deaf												
	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
1871	2	1	4	2	2	1	1	1	1	4	4	4	27
1872	2	2	0	1	3	1	2	0	3	1	1	1	17
1881	3	0	1	2	2	0	0	3	4	5	4	0	24
1882	4	2	2	3	4	2	0	1	2	3	0	1	24
1897	0	1	3	2	1	3	3	0	0	0	2	1	16
1898	2	5	1	3	3	3	2	4	1	3	0	2	29
1901	3	2	1	2	3	1	1	1	0	0	3	3	20
1902	4	3	1	3	4	1	2	3	0	3	0	0	24
1905	4	0	2	1	2	4	1	2	0	5	4	3	28
1906	4	1	4	1	2	3	2	1	6	2	2	4	32
1913	3	1	1	3	2	2	3	5	2	5	3	1	31
1914	5	3	4	1	5	0	0	2	2	4	3	2	31
1917	2	6	2	2	1	1	1	3	3	2	2	2	27
1918	2	3	4	4	2	2	1	4	5	4	2	4	37
1919	2	0	5	1	4	1	0	1	3	2	3	2	24
1935	3	1	0	2	0	1	1	2	1	3	1	6	21
1936	3	0	0	4	1	0	0	1	1	1	2	1	14
1943	2	1	0	0	0	0	3	3	1	3	4	1	18
1944	2	1	2	0	0	0	2	1	0	1	1	1	11

1941 epidemic in Australia was the employment of young woman in their early pregnancy in the services, munitions factories, offices and so on, where the herd was constantly being replenished with fresh recruits susceptible to rubella.

In Table VIII are given the numbers of births of the deaf for various institutions for the deaf in different countries by month. The Australian and New Zealand experience may be found analysed into epidemic and non-epidemic periods in *Lancaster* [1951b] and *Lancaster* and *Pickering* [1952]. Here they are shown combined for better comparison with the overseas countries. It is easily seen that except for Iceland and possibly the United States, none of the other countries show any notable concentration into particular months or season. We should expect the highest incidence in October judging by the incidence of rubella in Massachusetts (*Rutstein*, *Nickerson* and *Heald* [1952], *Aycock* and *Ingalls* [1946]) or by adding six months onto the Southern Hemisphere month of greatest incidence, April, or by noting the season of observed and reported cases of rubella anomalies reported in the literature. However, a convincing seasonal rise is to

be noted only in Australia, New Zealand and Iceland. It is absent from the English, Swedish and Italian birth figures. A small rise is apparent in the United States births of the deaf over the months September to January. When the Australian or the New Zealand experience is analysed into epidemic and non-epidemic years, it is found that there is no excess of births in the epidemic months, March to September, in the non-epidemic years (*Lancaster* [1951]). This would seem to indicate that sporadic cases of rubella deafness are numerous in neither Australia nor New Zealand (*Lancaster* and *Pickering* [1952]).

4. *Discussion.*

The world-wide survey, although necessarily incomplete, of deafness from census or institutional data has served to confirm the importance of isolation in the production of large epidemics of the disease—Iceland, Australia and New Zealand being the only countries with large epidemics of deafness. It would be desirable in this connection to examine the incidence in such areas as Hawaii and isolated areas

Table VIII. The Distribution of Births of the Deaf by Months.

Country	Approximate Years of Experience	The Number of Births by Month											
		Total	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Australia	1861–1946	2859	225	239	297	314	289	222	258	242	219	206	192	156
New Zealand	1890–1945	995	71	67	108	98	116	84	98	82	75	59	67	70
Iceland	1935–1947	24	2	0	1	3	1	6	3	1	4	2	1	0
Sweden	1900–1941	557	61	54	48	45	55	29	32	50	28	52	56	47
Italy	1875–1947	1343	118	105	126	118	108	107	104	105	103	130	115	104
England	1890–1949	3498	309	297	270	313	276	281	278	296	302	312	247	317
United States of America														
St. Louis, Mo.	1896–1948	551	49	40	48	35	43	37	39	31	56	57	62	54
Northampton, Mass. .	1846–1948	1650	145	120	136	122	135	124	128	147	145	169	124	155

in Northern Europe, where it would be possible to have epidemics of rubella in which large numbers of adults are infected.

The epidemiological inferences to be drawn from this paper and *Lancaster* [1951b] and *Lancaster* and *Pickering* [1952] are consistent with the following statements. Rubella in populous areas formerly was almost entirely a disease of childhood. If a country is isolated, rubella may die out and then when reimported it may attack individuals at all ages in the population. This, perhaps, has happened in Australia (*Scholes* [1944]). Among those attacked may be some pregnant females and so rubella deafness cases may occur. Even in populous areas with rubella continuously endemic improvements of hygiene have led to some females reaching adult life without having been infected. So that rubella is becoming an important factor in the production of deafness in such countries as England and Sweden. An unusually high incidence of rubella then may cause cases of congenital abnormality. Such a statement is consistent with what is known of the epidemiology of morbilli, *Lancaster* [1925]. It is necessary, however, to acknowledge the limitations of the methods used. They are capable of detecting only relatively large epidemics when only yearly birth figures are available, but are somewhat more sensitive if the births are given by month and year. A case in point is congenital anomalies such as ductus arteriosus, in which the methods were unable to detect a seasonal swing in New South Wales due to rubella (*Lancaster* [1951a]) although the methods were hampered then by not knowing the actual date of birth but only the date of death. The association of patent ductus and maternal rubella had already been reported by *Swan*, *Tostevin*, *Moore*, *Mayo* and *Black* [1943] and has since been studied by *Rutstein*, *Nickerson* and *Heald* [1952] who were able to illustrate the season incidence of congenital cardiac anomalies due to rubella. The methods would be more effective if cases of deafness of known etiology such as certain hereditary cases and cases occurring in the first few years of extrauterine life could be excluded. This refinement would not be practicable in a survey of a number of different countries. But the ultimate aim should be to assess the cause of deafness of every child entering institutions for the deaf in the light of modern knowledge. It would be desirable to have records of audiograms, physical examination and history of all persons ever to have received education from the institutions for the deaf in as many countries as possible.

Summary.

Further census and institutional data have been analysed. The only country other than Australia and New Zealand to have experienced deafness on a severe epidemic scale has been Iceland. Other countries investigated include the United Kingdom, the United States of America, Italy and Sweden. No dramatic epidemic episodes have been noted in these countries although the institutional data shows the sporadic cases that have occurred recently in the United States, in England and in Sweden. The importance of isolation in lengthening the time between epidemic waves of rubella has been stressed.

Résumé.

On a analysé les données du recensement et les renseignements obtenus dans les institutions. A part l'Australie et la Nouvelle Zélande le seul pays ayant fait l'expérience de la surdité sur une échelle épidémique est l'Islande. Parmi les autres pays examinés se trouvent le Royaume Uni, les Etats-Unis, l'Italie et la Suède. On n'a pas pu y constater d'épidémies dramatiques, mais les renseignements obtenus dans les institutions révèlent les cas sporadiques qui se sont produits récemment aux Etats-Unis, en Angleterre et en Suède. L'auteur souligne l'importance de l'isolement pour prolonger l'espace de temps séparant deux accès épidémiques de la rubéole.

Zusammenfassung.

Weitere Angaben aus Volkszählung und Anstalten wurden analysiert. Das einzige Land außer Australien und Neuseeland, welches in einem ernstlich epidemischen Ausmaße von Taubheit betroffen worden ist, war Island. Andere untersuchte Länder umfassen Großbritannien, die Vereinigten Staaten von Amerika, Italien und Schweden. Dramatisch-epidemische Ereignisse konnten hier nicht festgestellt werden, obgleich die Angaben von Anstalten die sporadischen Fälle aufzeigen, welche unlängst in den Vereinigten Staaten, in England und in Schweden aufgetreten sind. Hervorgehoben wurde die Bedeutung der Isolation für die Verlängerung des Zeitabschnittes zwischen epidemischen Wellen von Rubella.

Acknowledgements.

This paper is published with the permission of the Director-General of Health, Canberra.

I have to thank the directors of institutions who have been kind enough to send material to me—*Nils Malm*, Director, Manilla School for the Deaf-and-Dumb, Stockholm, Sweden; Dr. *Vilm Jónsson*, Director-General of Health, Reykjavik, Iceland; Dr. *Alessandro Gaddi*, Director, State Institute for the Deaf and Dumb, Rome; Mr. *S. R. Silverman*, Director, Central Institute for the Deaf, St. Louis, Mo.; Mr. *J. Spalding*, Headmaster, Royal Residential Schools for the Deaf, Old Trafford, Manchester, England; Mr. *F. W. Cockersole*, Headmaster, Royal School for Deaf Children, Church Road, Edgbaston, Birmingham; Miss *Louise A. Hopkins* of the Clarke School for the Deaf, Northampton, Mass.

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Nyholm, M. and *H. Fr. Helweg-Larsen*: Acta genet. 5, 25–38, 1954

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ON THE COMPUTATION OF MORBID RISK

(Disease Expectancy)

By MOGENS NYHOLM and HANS FR. HELWEG-LARSEN

By *morbid risk* we understand the risk at birth for developing a specified illness, previous to a certain age. Thus the morbid risk represents an age-corrected expression for morbidity of descriptive value in Public Health work in populations of different age-compositions, as well as in studying the morbidity in social groups differently related to an index-case.

However, morbid risk has been mainly applied in human genetic research in dealing with diseases of no obvious Mendelian inheritance and long manifestation period. In human genetics the computed figures may allow us to estimate an empirical genetic prognosis for relatives of a propositus, and in some cases permit induction as to the mode of inheritance in Mendelian terms.

Several varying methods of computing morbid risk have been designed [1, 2, 3, 4]. In using these methods at the University Institute for Human Genetics, Copenhagen, concerning bronchial asthma [5], mammary cancer [6], uterine cancer [7], gastric cancer [8], leukemia [9], mongoloid idiocy [10], pernicious anemia [11], diabetes mellitus [12], and psoriasis, we have been forced to examine the mathematical and statistical basis of the methods and to develop our ideas regarding the fallacies in, and applicability of the methods in practical genetic research.

We feel that the experience obtained in this work has clarified our methods of computing morbid risk, and we hope that by describing our present procedures we may possibly elucidate some problems for the human geneticist and Public Health worker, and perhaps contribute to attempts to standardize the various notations and methods in computing morbid risk.

I. Hypothetical Assumptions.

Dealing with morbid risk, we imagine some population groups delimited for instance by residence in a certain area, by sex, by race, by their proximity to an index case, or, in genetic research, by their relationship to a propositus.

The present authors have dealt mainly with morbid risk from the point of view of inheritance and we therefore prefer to discuss the topic with particular reference to medical genetics.

(a) We assume that in one of the population groups concerned a certain fraction, g, of the individuals will possess the possibility of contracting a certain chronic illness during a definite period of manifestation[1].

This period may perhaps comprise the total lifetime of the individuals (*e.g.* diabetes mellitus).

(b) The fraction g, which is the rate: potentially ill individuals

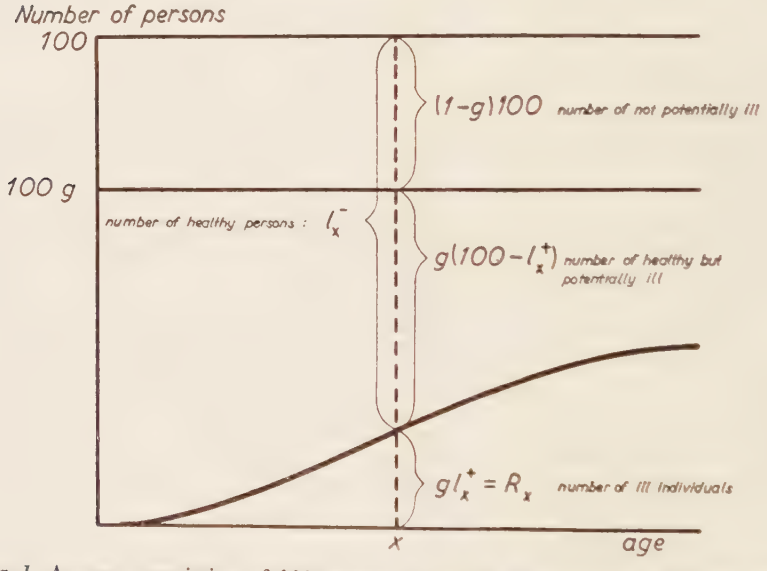

Fig. 1. A group consisting of 100 persons in which the fraction g of those born possesses the possibility of contracting an illness. At the age x is indicated the number of ill persons and the number of healthy individuals, potentially ill and not potentially ill, respectively.

[1] For convenience we deal with a chronic illness. It is possible, of course, to compute the risk of a second attack of some disease. The mathematical expressions for diseased persons are then to be understood as referring to such of them as have or have had the disease for the second time.

divided by all live born, may vary from one group to another but in genetic research it is assumed to be constant from generation to generation.

(c) Further, the age-distribution of the ill persons at the moment of manifestation is assumed to be identical for the different groups, and independent of time, apart from the influence of varying mortality and migration of the groups.

Imagining a correction for the influence of mortality, other diseases than that investigated, migrations etc., we introduce the following notations:

(d) Of those persons born with the possibility of contracting the illness concerned, 1_x^+ per cent are expected to have done so at the age x.

In a group in which the fraction g of those born possesses the possibility of contracting the illness, $g \cdot 1_x^+$ per cent will be ill, $g(100-1_x^+)$ per cent will be healthy but potentially ill, and $(1-g)\cdot 100$ per cent will be healthy and not potentially ill at the age x.

(e) The percentage of healthy individuals among all persons at the age x is called 1_x^-.

Thus we have:

$$\begin{aligned} 1_x^- &= g\,(100-1_x^+) + (1-g)\cdot 100 \\ &= 100 - g\cdot 1_x^+ \end{aligned} \tag{1}$$

(f) If μ_x denotes the intensity with which the illness appears among the healthy individuals at the age x, we have, according to an elementary life insurance formula [13]:

$$1_x^- = 100 \cdot e^{-\int_0^x \mu_y \, dy} \tag{2}$$

(g) The morbid risk, expressed in per cent, *i.e.* the probability at birth of contracting a specified illness previous to some age limit x, the individual being supposed to live up to that age limit, is denoted R_x.

From the assumptions (d) and (g) we obtain:

$$R_x = g \cdot 1_x^+, \tag{3}$$

and from equations (1), (2), and (3), we obtain:

$$R_x = 100 - 100 \cdot e^{-\int_0^x \mu_y \, dy} \tag{4}$$

[1] e denotes the base of the natural logarithm.

Generally, it is not possible to estimate the ratio of potentially ill persons at birth, g, directly from the observations, but the morbid risk, R_x, may be estimated. According to (3), the fraction g in different groups will be proportional to the morbid risks R_x.

II. Estimation of the Morbid Risk in Observed Samples of Populations.

Usually we try to procure the following information about the population groups (groups of relatives):

Number of individuals living in the different age intervals at the time of the investigation.

Number of individuals deceased in specified age intervals previous to the investigation.

For both the above categories, the number of individuals who contracted the illness concerned in specified age intervals.

Furthermore for a major population, we often possess information as to the age-specific incidence[1] (or age-specific prevalence) of the illness concerned during a certain period (or at the time of investigation), as well as the age sex composition of the total population.

The problem now is to estimate the morbid risk (R_x) based on this information, and to control some of the assumptions made if possible.

We have to distinguish between two extreme cases:

(A) The diseased persons do not have any excessive mortality (*e.g.* lymphedema, cataract, glaucoma, multiple exostoses, periodic paralysis, otosclerosis etc.). During the computation of risks they are therefore treated similarly to healthy individuals.

(B) They die immediately after having contracted the illness (*e.g.* malignant neoplasms).

The formulae for the computation of morbid risk is different in each case. However, material of type (A) and intermediate types may be transformed to (B) if the diseased persons are excluded immediately after having contracted the illness, as if they had then died. On the other hand by means of a Survivorship Table it is also possible with material of type (B) to compute the number of person-years the ill persons ought to have shown provided they had the same mortality as the general population. The estimated number of person-years is then used in a computation of type (A).

[1] Number of attacks of disease or disability recorded at specific ages ÷ total population from which the information is drawn at specific ages.

In both cases the manifestation period is divided into age intervals small enough so that the biometric functions (R_x) are approximately linear and the ages of the observed individuals approximately evenly distributed within the intervals. The intervals do not necessarily have to be equidistant. For ease of presentation, however, in the following formulae the width of the interval is conceived as a constant h.

The following notations are now introduced for the observed numbers in a population group:

(h) L_x denotes the number investigated, who, at the time of the investigation, were in the age interval $x-h/2$, $x+h/2$.

Persons who died or emigrated prior to the investigation are counted as if they had been examined when they died or emigrated.

(j) L_x^+ denotes the number of ill individuals among L_x.

(k) $L_{x,\infty}$ denotes the number of persons examined in the age intervals from $x+h/2$ to infinity plus half the number in the age interval $x-h/2, x+h/2$. In other words $L_{x,\infty}$ denotes the number of persons examined who have passed the age x at the time of the investigation. Expressed in symbols:

$$L_{x,\infty} = 1/2\, L_x + \Sigma L_y \tag{5}$$

(ν assumes the values: $x+h$, $x+2h$,... up to the end of the manifestation period).

(l) Finally, A_x denotes the number of persons who contracted the illness during the age interval $x-h/2$, $x+h/2$.

We are now able to discuss the computation of the morbid risk according to the type of mortality of the illness concerned.

(A) *The diseased persons have no excess mortality.*

Considering the first type of illnesses, we expect the ratio of those who have contracted the disease previous to age to the total exposed to the risk to be $R_x/100$. If this fraction is multiplied by the number of persons examined during the interval $x-h/2$, $x+h/2$, we obtain the expected number of diseased persons to be found in that interval:

$$E\left\{L_x^+\right\} = \frac{R_x \cdot L_x}{100} \tag{6}$$

Further, when a cohort of persons pass from the age $x-h/2$ to $x+h/2$, the morbid risk increases from $R_{x-h/2}$ to $R_{x+h/2}$. Thus

[1] E { } denotes an expected quantity.

we expect that $R_{x-h/2} - R_{x-h/2}$ per cent of those passing the interval contract the illness. We may also express this as the expected incidence rate during the interval: $R_{x-h/2} - R_{x-h/2}$ per cent. The particular cohort comprises $L_{x,\infty}$ persons. Therefore we expect the number of persons in the group contracting the illness during the interval to be the incidence rate multiplied by the total number of persons exposed to risk during the interval (cf. 1):

$$E\left(A_x\right) = \frac{R_{x+h/2} - R_{x-h/2}}{100} L_{x,\infty} \tag{7}$$

or the expected incidence rate during the interval will be:

$$E\left(\frac{100\ A_x}{L_{x,\infty}}\right) = R_{x+h/2} - R_{x-h/2}. \tag{8}$$

If we sum the individual incidence rates or the differences in morbid risk for each age interval we obtain the morbid risk up to a certain age x:

$$R_x \simeq 100 \sum \frac{A_y}{L_{y,\infty}} \tag{9}$$

Here, and wherever nothing different is stated we conceive that y assumes values corresponding to the midpoint of the intervals in the manifestation period up to x−h 2. If we prefer to limit our computations at a definite high age, denoted c, we sum up to c−h 2. (c may be selected at a point when the manifestation period seems to have passed its upper limit).

The variance[1] of the incidence rate during the age interval x−h 2, x+h 2 is estimated as for other rates, being:

$$\mathrm{Var}\left(\frac{100\ A_x}{L_{y,\infty}}\right) = \frac{(R_{x-h/2} - R_{x-h/2})\ (100 - R_{x-h/2} - R_{x-h/2})}{L_{x,\infty}} \tag{10}$$

This formula requires:

(m) that the attacks of illness occur independently of each other.

This assumption will generally only be fullfilled approximately in genetic research, where we meet with several diseased relatives of the same propositus. We shall not discuss interdependence between attacks of illness further in this paper, but the dependence will increase the variance. At least some of this increase will be met by using a quantity somewhat greater than (10), namely:

$$\mathrm{Var}\left(\frac{100\ A_x}{L_{x,\infty}}\right) = \frac{(R_{x+h/2} - R_{x-h/2})\ 100}{L_{x,\infty}} \simeq \frac{100^2\ A_x}{(L_{x,\infty})^2} \tag{11}$$

[1] *I.e.* the square of the standard deviation of the rate. (Binomial distribution is assumed.)

However, the main reason for the substitution is to facilitate the computation of the variance of the incidence rate.

In order to obtain the variance of the estimated morbid risk, R_x, we sum the individual variances of the incidence rates of the different age intervals:

$$\mathrm{Var}\left\{100\ \Sigma\frac{A_y}{L_{y,\,\infty}}\right\} \simeq 100^2\ \Sigma\frac{A_y}{(L_{y,\,\infty})^2} \tag{12}$$

Obviously, (12) shows that the variance of the estimate of R_x becomes large when $L_{x,\,\infty}$ is small in some of the age intervals. Sometimes it is therefore a practical procedure to disregard the highest, poorly populated age intervals, and to compute the morbid risk only up to a certain age (c, *vide* page 30).

(*B*) *The illness involves immediate death*[1].

In the case of immediate death after onset of the illness[2] it is no longer true that the expected number of diseased persons in an age interval equals the morbid risk at the midpoint of the interval multiplied by the total number of persons in that interval, in extreme cases there are no diseased people at all. Thus the equations (6)–(9) do not hold any longer. However, the number (A_x) of persons contracting the illness during the interval $x-h/2$, $x+h/2$ is identical with the number of ill individuals (L_x^+) observed among L_x persons during the interval concerned, thus:

$$L_x^+ = A_x \tag{13}$$

The expected number of attacks during the interval must be the intensity with which they occur during the interval (μ_x), multiplied by the span of the interval (h), and further multiplied by the number of persons passing the interval ($L_{x,\,\infty}$):

$$E\left\{A_x\right\} = h \cdot \mu_x \cdot L_{x,\,\infty}, \text{ or} \tag{14}$$

$$h \cdot \mu_x \simeq \frac{A_x}{L_{x,\,\infty}} \tag{15}$$

Thus equation (15) gives the incidence of the illness during the interval concerned.

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[1] In his review [14] of *Schwartz:* Heredity of Bronchial Asthma [5], *Böök* erroneously assumes that *Schwartz* has used this previously common method. However, *Schwartz* has actually used the method mentioned in Section A (page 29) in this paper.

[2] "Immediate" must be understood in a practical sense—if the age intervals comprise 10 years, death after less than one year of illness may be conceived as "immediate".

Returning to equation (4) and assuming that μ_x is linear within the intervals, we obtain:

$$R_x = 100 - 100 \cdot e^{-\Sigma h \cdot \mu_y}$$

and substituting according to (15):

$$R_x \simeq 100 - 100 \cdot e^{-\Sigma \frac{A_y}{L_{y,\infty}}} \tag{16}$$

Using the logarithmic form of (16) we obtain:

$$\log (100 - R_x) \simeq 2 - 0.4343 \, \Sigma \frac{A_y}{L_{y,\infty}} \tag{17}$$

This expression is used in the computation of the morbid risk when the illness involves immediate death.

Similarly to the derivation of the estimate of the variance in case A, (12) we first obtain the estimate of $\log (100-R_x)$:

$$\mathrm{Var} \left\{ 2 - 0{,}4343 \, \Sigma \frac{A_y}{L_{y,\infty}} \right\} = 0{,}4343^2 \, \Sigma \frac{A_y}{(L_{y,\infty})^2} \tag{18}$$

From equation (18) we then obtain[1] the approximate variance of the estimated R_x:

$$\mathrm{Var} \left\{ 100 - 100 \cdot e^{-\Sigma \frac{A_y}{L_{y,\infty}}} \right\} \simeq (100 - R_x)^2 \, \Sigma \frac{A_y}{(L_{y,\infty})^2} \tag{19}$$

Use of information from the general population.

The large general population, to which the groups mentioned belong, sometimes exists analyzed as to the yearly, age-specific incidence rate for different illnesses, particularly those which involve approximately immediate death, such as certain types of malignant tumors. If the incidence rates are multiplied by h expressed in years we obtain the incidence during the age interval selected for our studies:

$$A_x/L_{x,\infty}.$$

Having obtained the incidence rate specific for our interval, it is possible to estimate the morbid risk (R_x) using equation (9) or (17), depending on the absence or presence of excess mortality in the illness concerned.

Occasionally, when we do not have the age-specific incidence rate, we may have the age-specific prevalence obtained by a special

[1] Using the general formula: $\mathrm{Var} \{ q(x) \} \simeq [q'(\xi)]^2 \, \mathrm{Var} \{ x \}$ (Hald [15], p. 97).

survey. In this case we get an estimate of the proportion L_x^+ to L_x and then, if the illness has no excess mortality, we have by (6):

$$R_x \simeq \frac{100\, L_x^+}{L_x}$$

This estimate of R_x only takes into account the persons who are between the ages $x-h/2$ and $x+h/2$. That is because the age distribution of the onset of illness is not known. On the other hand, the estimates of R_x for different ages might together give a better estimate for a specific age, using the fact that R_x increases with increasing age.

The estimated morbid risk (R_x) for the general population will most often only be influenced by a diminutive sampling error compared to the estimated morbid risk obtained from the data of the groups actually examined. The information from the general population may, however, be used to improve our estimate of R_x for the smaller groups. This procedure was first suggested by *Strömgren* [3] in estimating the morbid risk for schizophrenia.

In this paper we want to present his procedure using our assumptions and symbols. First, we distinguish the notations for the general population and the smaller group by adding an apostrophe to the latter.

Next, we assume that the fraction of those born with the possibility of contracting the illness is g in the general population, and g' in the group. According to equation (3) we have:

$$R_x' = \beta R_x \quad (\beta = g'/g = \text{constant}). \tag{20}$$

Our estimate of β, denoted b, is determined so that by computing the expected total number of ill persons $\Sigma\, E\,\{A'_{yj}\}$ by b and expressions for the age-specific incidence in the general population, R_y and L'_y, we obtain the observed number of diseased individuals: $\Sigma\, A'_y$.

A. No excess mortality.

Considering the case in which the illness involves no excess mortality, we may estimate the morbid risk up to a definite age, denoted c.

From the equations (7) and (20) we then obtain:

$$R_c' = \beta R_c \frac{100\, E(A_x')}{\beta (R_{x\,-\,h/2} - R_x + h/2)\, L_{x,\,\infty}'}$$

$$R_c' \simeq \frac{100\, A_y'}{1/R_c\, (R_{x\,-\,h/2} - R_x + h/2)\, L_{x,\,\infty}}$$

By summation we obtain the estimated morbid risk of the smaller group up to age c:

$$R'_c \simeq \frac{100\,\Sigma A'_y}{1/R_c\,\Sigma (R_{y\,+\,h/2} - R_{y\,-\,h/2})\,L'_{y,\,\infty}} \tag{21}$$

The equation (21) may be expressed more simply when the collected material of the smaller group is rearranged so that the individuals investigated at a higher age than c are listed as if they were examined immediately previous to that age. From (6) and (20) we then obtain the morbid risk of the smaller group at age c:

$$R'_c \simeq \frac{100\,L'^{+}_x}{\frac{R_x}{R_c} L'_x}$$

and by summation we obtain the estimated morbid risk of the smaller group up to age c:

$$R'_c \sim \frac{100\,\Sigma L'^{+}_y}{\frac{1}{R_c}\,\Sigma R_y L'_y} = \frac{100\,\Sigma A'_y}{\frac{1}{R_c}\,\Sigma R_y L'_y} \tag{22}$$

b (the estimate of β) is found by dividing the estimated R'_c by R_c. For an arbitrary age we obtain:

$$R'_x \simeq b\,R_x \tag{23}$$

Concerning the variance of the estimated morbid risk up to age c. we have, according to (6):

$$\mathrm{Var}\left\{100\,L'^{+}_x\right\} = R'_x\,(100 - R'_x)\,L'_x;$$

consequently

$$R'_x\,L'_x\,(100 - R'_c) < \mathrm{Var}\left\{100\,L'^{+}_x\right\} < 100\,R'_x\,L'_x$$

(because $R_c > R'_x$).

By summation, we obtain:

$$(100 - R'_c)\,\Sigma R'_y L'_y < \mathrm{Var}\left\{100\,\Sigma A'_y\right\} < 100\,\Sigma R'_y L'_y.$$

or, denoting the numerator and the denominator in the estimate for R'_c (21) or (22) N and D:

$$\frac{(100\,D - \Sigma R'_y L'_y)\,\Sigma R'_y L'_y}{D} < \mathrm{Var}\left\{100\,\Sigma A'_y\right\} < 100\,\Sigma R'_y L'_y$$

The expression $\Sigma R'_y L'_y$ being the expected value of N, we find that the variance of the estimated morbid risk of the smaller population R'_c generally will be smaller than $100\,N/D^2$ and larger than $N\,(100\,D - N)\,/\,D^3$.

For ensuring safety in comparisons it is generally advisable to use the highest estimate of the variance. Thus we have:

$$\text{Var}\left\{\text{Estimated } R_c'\right\} < \frac{100\ R_c'}{D} \simeq \frac{(\text{Estimated } R_c')^2}{\Sigma A_y'} \tag{24}$$

Then we obtain the variance of the estimated R_x' by (23)

$$\text{Var}\left\{\text{Estimated } R_x'\right\} < \frac{100\ R_x'^2}{R_c'\ D} \simeq \frac{(\text{Estimated } R_x')^2}{\Sigma A_y'} \tag{25}$$

(Summation up to c−h/2).

The reader will notice that the percentage error of the estimates of R_c and R_x decreases when c approaches the end of the manifestation period.

B. Excess mortality.

According to the equation (20) a constant ratio β exists between R_x' and R_x. Contrarily the ratio between μ_x' and μ_x varies with age. According to (4) we have:

$$-\int_0^x \mu_y'\, dy = \log_e (100 - R_x') - \log_e 100$$

Using the equations (4) and (20) we obtain by differentiation:

$$\mu_x' = \frac{\beta}{100 - \beta R_x} \frac{dR_x}{dx}$$

$$\mu_x' = \beta\mu_x \frac{100 - R_x}{100 - \beta R_x} \tag{26}$$

$$= \beta\mu_x + (\beta - 1)\ \beta\mu_x R_x 10^{-2} + (\beta - 1)\beta^2 \mu_x R_x^2 10^{-4} + \ldots \tag{27}$$

Generally, it will be sufficient to use the first two or three items of this series. If three items are used, the following quantities are computed:

$$h\,\Sigma\,\mu_y\,L_{y,\,\omega},\quad 10^{-2}h\,\Sigma\,\mu_y R\ L'_{y,\,\omega} \text{ and } 10^{-4}h\,\Sigma\,\mu_y R_y^2 L_{y,\,\omega}'$$

Next, b is found by trial and interpolation from the formula:

$$b\,h\,\Sigma\,\mu_y L_{y,\,\omega}' + (b-1)b\,10^{-2}\,h\,\Sigma\,\mu_y R_y L_{y,\,\omega}'$$
$$+ (b-1)b\,10^{-4}h\,\Sigma\,\mu_y R_y^3 L_{y,\,\omega}' = \Sigma\,A_y'.$$

The following may be used as an initial value for b.

$$b = \frac{\Sigma\,A_y'}{h\,\Sigma\,\mu_y L_{y,\,\omega}'}$$

When b is found, the intensity with which the illness occurs at age x in the smaller group, μ_x', may be estimated according to the equation:

$$\mu_x' \simeq b\mu_x + (b-1)b\mu_x R_x 10^{-2} + (b-1)b^2 \mu_x R_x^2 10^{-4} \tag{28}$$

The morbid risk of the smaller group up to age x (R_x) and the variance of this expression may be estimated according to (23) and (25).

III. Control of Assumptions.

Generally there are no difficulties in computing an estimate of the morbid risk (R_x), and the corresponding variance, but in using these estimates we depend completely on the validity of our assumptions.

We will try to show some control procedures which are easily carried out—unfortunately they do not indicate deficiencies in the assumptions, different biases counteracting each other or having similar effects in the groups compared. However, the extent of these counteractions may be different for various groups of the population.

A moderate excess of mortality among the diseased individuals will involve a higher morbid risk for those deceased at the time of the investigation than for those who were alive. This may be counteracted by the fact that information about the deceased is less complete than for the others. This counteraction will be most pronounced for groups distantly related to the propositus.

An increase of the morbid risk with time will involve a higher risk for sibs than for parents, and for children compared to sibs of the propositus.

In genetic research the ratio between the morbid risks (R_x) for different groups of relatives ought to be independent of age. This assumption is checked by drawing the estimate of R_x against age. If the assumption cannot be accepted there is reason to beware of deficiencies in other assumptions:

Information lacking in cases of illness in distant groups of relatives will mean that the estimated morbid risk will increase comparatively slowly, especially in the younger age-groups, which usually show this deficiency most frequently.

Having obtained the estimated morbid risk (R_x) for the general population, it is worth while to check this estimate against the estimated morbid risks for the smaller groups (R_x) by plotting R_x against R_x. Assuming there is a constant ratio between R_x and R_x independent of age the resulting graphs would be straight lines through the zero point if the assumption is valid.

If *Strömgren's* method [3] has been used, the hypothetical distribution of the age-specific incidence of the cases is easily computed

according to equations (7) or (14). This hypothetical age-distribution of the incidence may be checked against the observed age-distribution of the incidence by a chi-square test, for instance.

IV. Comparison of the Ratio of the Potentially Ill Persons at Birth for Different Groups.

Among the assumptions (section I) we mentioned that we are able to obtain an estimate of the ratio (denoted g) of potentially ill individuals to all those live-born only if all cases of the illness concerned show up previous to a definite age. This assumption is generally not fulfilled, but the ratio between the morbid risks for two compared groups (R_x') will reflect the corresponding ratio between the rates: potentially diseased individuals ÷ all live births (g'). Assuming that the observations for two different groups are stochastically[1] independent, the estimated morbid risks (R_x' or R_x) for the groups may be compared by a u-test[2], dividing the difference between the morbid risks by the square root of the sum of their variances.

In genetic research the problem may arise whether the values of g' in n groups form given proportions $p_1, p_2, p_3, \ldots p_n$, according to the *Mendel*ian laws. We may test this hypothesis if one of the age-intervals (as defined in section II) comprise enough observations to allow a chi-square test by comparing the observed distribution of the disease with the hypothetical. In Case A, with no excess mortality for the diseased persons, denoting the individual group ν and by summing from $\nu = 1$ to $\nu = n$, we obtain according to (7):

$$\chi^2_{f=n-1} = \Sigma \frac{\left(\frac{p_\nu L_{x,\nu,\infty}}{\Sigma p_\nu L_{x,\nu,\infty}} \Sigma A_{x,\nu} - A_{x,\nu}\right)^2}{\frac{(p_\nu L_{x,\nu,\infty}) \Sigma A_{x,\nu}}{\Sigma p_\nu L_{x,\nu,\infty}}} \qquad (29)$$

The same formula can be used in cases of excessive mortality providing that values of $\mu_{x\nu}$ are approximately proportional to the values of p_ν' (compare (20) and (26)). The chi-squares for the different age-intervals not being independent, they cannot be summed to a total chi-square value.

In this formula, we have assumed that the observations from the different population groups are stochastically independent. For

[1] *I.e.* the probability of an event in one group is independent of whether or not an event in the other group has occurred.

[2] Significance levels as for t-test.

groups of relatives, however, it may often be found that the deviations between the number of cases observed and the hypothetical number tend to have the same direction in the different groups. However, this correlation will not increase the computed values of u or χ^2, and the test will therefore still be useful.

Summary.

The computation of morbid risk (disease expectancy) for diseases appearing during a manifestation period is discussed with particular regard to the influence of excess mortality of the disease concerned.

Résumé.

Discussion du calcul du risque de morbidité pour maladies se développant pendant une période de manifestation. On a tenu compte surtout de l'influence de la surmortalité de la maladie en question.

Zusammenfassung.

Die Berechnung der Erkrankungsgefahr (Krankheitserwartung) bei Krankheiten, welche während einer Manifestationsperiode auftreten, wird besprochen unter besonderer Berücksichtigung des Einflusses von Übersterblichkeit durch die betreffende Krankheit.

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Wrighton, R. F.: Acta genet. 5, 39–63, 1954

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AUXILIARY RANDOMISATION

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1. Introduction.

In an earlier communication[1] the writer discussed the formal structure of a statistical experiment in which the theory of probability was concerned solely as a result of the introduction of an auxiliary randomising device. The object of the present paper is to outline the principles needed for constructing such devices in adequately designed sampling experiments. A fresh approach is necessary because methods of randomisation customarily recommended are never related in this way to specific problems and moreover, perhaps as a consequence of this, rely on assumptions with respect to the foundations of probability theory which have never been universally accepted. These assumptions in part have given rise to and in part reflect four conceptions of randomness, which for convenience we label as follows:

(i) *The classical conception of randomness.* Here randomness is regarded as essentially subjective and connotes the absence of purposeful selection. The word *random* was often used in this sense by the classical writers on probability theory. Investigations carried out on the basis of this conception are widely felt to be in accordance with the legitimate dictates of commonsense; but their logical basis has been repeatedly attacked.

(ii) *The static conception of randomness.* Here the adjective random is dissociated from physical *procedures* of arbitrary selection and instead is used to describe the disordered *states* which may result from such procedures. "Randomness" in this sense may be equated with "disorder". Mathematically this conception of randomness is more closely connected with arithmetic and the theory of numbers than with the theory of probability.

[1] This journal, 1953.

(iii) *The empirical conception of randomness.* This requires that the validity of a random process should depend on the knowledge that in the past it has consistently reproduced predicted frequencies in extended trials. It has been developed most fully in the present century by *R. von Mises* but previously it had been necessarily adopted in some form by all statistical schools of probability theory.

(iv) *The aleatory conception of randomness.* This regards random selection as selection following upon the shuffling of definite physical entities. It was this conception which stimulated the initial mathematical investigations into the theory of probability and it is the one which we shall adopt here. We shall aim to design shuffling procedures which are thorough; and insofar as we succeed we shall approach the ideal of a perfectly random process.

Of the first three of these approaches to the specification of randomness the empirical is the most important to us since it is the one which might be most plausibly developed for the purpose we have in hand; and, in particular since it comes closest to the approach which will be advocated in the present paper, it will be useful to set out the precise respects in which it falls short of our requirements. The static approach is less directly important since from the outset it deals with a class of problems which is essentially alien; but since its influence is often present, if unrecognised, in current treatments of the problem of random sampling, it merits some consideration here. The classical approach does not seriously concern us because it is widely regarded as inadequate and because any system we eventually develop must more than satisfy the conditions it calls for. In one way however it is important. It continually recurs as the commonsense approach to a variety of problems and adds to the plausibility of other theories when used coinjointly with them. We shall consider some of its practical implications at the end of this paper. Its logical status in respect of the problem of auxiliary randomisation is negligible and for the moment we confine our attention to the empirical theory and to the static theory.

2. The empirical theory of randomness.

We consider first some of the implications of the empirical theory as propounded by *von Mises*. This theory is primarily concerned with naturally-occurring randomness and does not necessarily have direct bearing on the primary problem we have under discussion. It is,

however, often argued that phenomena which the theory regards as random may conveniently and properly be used for auxiliary purposes in unrelated fields. One of our chief contentions here is to be that the elaboration of artificial randomness is a problem *sui generis* and in examining the theory of *von Mises* we shall find support for this opinion.

From the outset *von Mises* regards probability as a purely synthetic concept, arising because of the experience we have of certain natural phenomena. In a particular situation we must arrive at the numerical measure of a probability by actual experiment; accordingly it is necessary to accept some form of frequency theory. From this *Venn*'s[1] requirement follows: a probability is only to be recognised within a sequence of recurrent events which is of indefinitely protractable length. The probability of occurrence of a particular event within such a sequence is defined as the value to which the ratio of the number of occurrences of this event to that of all events in the sequence tends: if a limit is *not* approached we cannot regard the sequence as random. If, however, a limit appears to exist we are still unable to associate the theory of probability with the system, for with this requirement alone strictly determinate sequences (such as that afforded by the regular alternation of head and tail) might be taken to be stochastic. Accordingly *von Mises* introduces a new requirement; in order to be regarded as a probability the limit characteristic of a sequence should not be alterable by any system of selection within the sequences which yields an indefinitely protractable subsequence; the only limitation imposed on such a system is that successive individual selections must be independent of a knowledge of the outcome of the particular trial open to acceptance. So, for example, in a sequence obtained by tossing a coin a putative probability, .5, of recording a head is to be rejected if the limiting frequency of heads obtained by rejecting every second trial differs from .5 or if the sequence derived from the original sequence by selecting only trials following the recording of a head possesses a limiting ratio which is similarly aberrant.

The requirements of the theory of *von Mises* are then, a sequence of recurrent events unlimited in duration, and the existence within this sequence of a unique limiting ratio which is the same for all subsequences obtained by what is referred to as *place-selection*. We proceed to examine three objections to the erection of a statistical theory on this foundation. These objections concern firstly the sta-

[1] See *The Logic of Chance*, chapter VI.

bility of empirically ascertained frequency-ratios, secondly the nature of the verificatory procedure called for in assessing the relevance of the theory in particular circumstances and thirdly the utility and possible consistency of calculations based on the theory.

(i) *The stability of limiting frequency-ratios.*

We cannot in *von Mises*' theory assert *a priori* the numerical value of any probability; for example, we cannot ascribe without experiment a probability of $^1/_6$ to the event of a six being thrown with a common die. However intuitive an idea of probability as frequency we have, this requirement is reasonable, since recorded trials with necessarily imperfect dice show that theoretically indicated frequencies are seldom approached in repeated trials; moreover, although carefully made dice may be expected to produce results more in accordance with expectation, we have no reason to suppose that prolonged experimentation would not still reveal persistent, if smaller, discrepancies. *Von Mises* represents the situation as follows (op. cit., p. 17):

> I have here two pairs of dice which are apparently alike. By repeatedly throwing one pair, it is found that the relative frequency of the "double 6" approaches a value of 0.028, or $^1/_{36}$ as the number of trials is increased. The second pair shows a relative frequency for the "12" which is four times as large. The first pair is true, the second, biassed, but our definition of probability applies equally to both pairs. ...In fact, it can be shown that if we throw one of the dice belonging to the second pair, the relative frequency with which a single 6 appears is about $^1/_3$, whereas for either of the first pair this frequency is almost exactly $^1/_6$th. In order to realise clearly what our meaning of probability implies, it will be useful to think of these two pairs of dice as often as possible: each pair has a characteristic probability of showing "double 6" but these probabilities are widely different... The probability of a 6 is a physical property of a given dice and is a property analogous to its mass, specific heat, or electrical resistance.

This assumed innate and numerically specifiable quality of a biassed die at once presents itself as a suitable matter for factual enquiry. The crudest demonstration will throw doubt on the validity of the notion. The writer, for example, loaded six dice and on three occasions threw them a hundred times, with the following results:

	pips observed					
	1	2	3	4	5	6
1st trial	46	94	118	80	99	163
2nd trial	45	70	91	106	108	180
3rd trial	54	92	103	78	96	178

Repeating the procedure, but reducing the distance which the dice were thrown after agitation reduced the bias in favour of *six* in each series as follows:

	pips observed					
	1	2	3	4	5	6
1st trial	74	96	102	91	86	151
2nd trial	68	106	120	85	84	137
3rd trial	63	86	111	96	92	152

Given a more extensive number of trials, we might well ask in respect of these dice which set of limiting proportions should rightly represent the *physical property* to which *von Mises* refers. It might be suggested that the question is irrelevant; that the electrical resistance of an object cannot be properly defined unless its temperature is given and that *von Mises* may be assumed legitimately to presuppose in the same way an exact specification of the physical circumstances under which his dice are thrown. But taken literally this contention at once loses its force. For an *exact* definition of the circumstances attendant upon the individual throw will reduce the problem to deterministic terms, all suggestion of probability and uncertainty disappearing. It seems impossible to specify adequately conditions for the stability of a frequency ratio if we are to rely on purely empirical means for establishing its numerical value.

(ii) *The verification of stochastic hypotheses.*

The empirical theory is especially attractive when the acceptance of a stochastic hypothesis must depend on the evidence afforded by an established body of data. This is the situation commonly met with by the working statistician. *Von Mises* writes (*op.cit.*, p. 33).

> Everybody who has been to Monte Carlo, or who has read descriptions of a gambling bank, knows how many "absolutely safe" gambling systems, sometimes of an enormously complicated character, have been invented and tried out by gamblers; and new systems are still being suggested every day. The authors of such systems have all, sooner or later, had the sad experience of finding out that no system is able to improve their chances of winning, i.e. to affect the relative frequencies with which different colours or numbers appear in a sequence selected from the total sequences of the game. This experience forms the experimental basis of our definition of probability.

In roulette a large margin of safety is allowed by the banker and there is no reason to suppose that systems have not been invented

and employed, successfully altering relative frequencies but failing to modify them sufficiently to enable the gambler to win consistently. This, however, is a minor point. It is more important to note that *von Mises*' view implies that a sequence must be regarded as random up until the time when evidence is produced which shows that this is not so. What reason however is there, other than mathematical convenience, for granting precedence to stochastic hypotheses in this way? Moreover who is to decide upon the *extent* of the preliminary investigations which must be carried out before a phenomenon is to be conditionally regarded as random? This latter question is of the utmost importance in considering the problem of elaborating artificial randomness; for here we cannot reasonably rely on the experience of previous investigators since this will certainly not have been related in any way to our own peculiar needs. More explicitly, this experience will have been arbitrary in two ways; firstly in respect of the range of place-selections assayed and secondly in respect of the number of trials on which each of these assays will have been based. *Von Mises* offers no grounds on which either of these matters can be profitably discussed. His notion of randomness rests essentially on a dialectical view of the relation between hypothesization and verification which, while at one level perhaps open to discussion, is too contentious to be arbitrarily assumed in a definition of probability.

But under this same heading there is another inadequacy of the empirical view. If we wish to use the concept of randomness not as the basis of a physical theory but in relation to sampling problems we have no reason for hoping, nor have we the need to demand, that the random process used should be theoretically perfect, in the sense that it should generate limiting frequencies, all of which reflect with perfect precision theoretical values. It is as unreasonable to suppose in applied probability theory that a perfectly random sequence exists as to suppose in applied geometry that a perfect circle or a perfectly straight line exists. *Von Mises* however does not explicitly allow for this. Seemingly the hypothesis of randomness is rejected when *any* deviation from the fundamental limiting frequency is detected in subsequences. The arbitrary nature of the extent of verificatory procedures employed is made doubly manifest by this. For, knowing that if he is sufficiently persistent a discrepancy is bound eventually to be revealed, an investigator will be the less inclined to protract beyond a convenient limit his actual attempts to disclose it.

(iii) *The nature of a statistical calculus based on the theory.*

Suppose however that we may ignore these first criticisms. If we consider the mode of elaboration of a probabilistic calculus which is to rest on *von Mises*' theory as a foundation we shall find that it can embrace none of the concepts commonly used in statistical theory. We need consider only the role of estimation procedures in such a system. In the case of an isolated collective their use is clearly superfluous. For the mode of establishment of the irregularity of the collective will *a fortiori* provide a sufficiently accurate estimate of the probability-parameter characteristic of it. Estimation within the irregular collective considered as a self-sufficient synthetic concept is therefore irrelevant to statistical enquiry in precisely the same way as the syllogism is to taxonomical enquiry; and the same stricture must be applied to any mathematical manipulation of probability values which rely entirely on empirical assessment. It is reinforced if we note that every manipulative procedure employed may exploit a departure from randomness not detected by systems of place-selection which have been antecedently assayed[1].

If, however, more than one putative collective were under consideration it might be suggested that the existence of randomness should be inferred by analogy and that on this procedure a formal system could be properly based. But certainly in operational fields where *ad hoc* methods are required for isolated problems (as will be common for example in medical and sociological applications) the procedure will not readily be justified. If we admit it, we admit a principle as far-reaching as the original empirical postulates of the theory which at once loses its pretensions to self-sufficiency.

The purpose of this critique has not been to deny that in many fields recording of the proportionate frequencies with which certain events occur is valid and useful; for it is plainly possible to retain this view without holding that the rationale governing such investigations depends on the theory of probability. We may consistently hold that their aim is the *measurement* of frequencies *per se* rather than the *estimation* of hypothetical probability-parameters. The distinction is of particular importance in considering the comparative statistical trial. In that type of experiment, as in all sampling experiments, we should aim to *estimate frequencies*. Values of probabilities are not in question since all of them will have been fixed *a priori*. This, we would

[1] *Cf. G. Spencer Brown*, Nature (1953), p. 154.

claim, is characteristic of the scientific application of probability theory and we put forward as a general principle that *the only unrestrictedly manipulatable probabilities are those which can in some sense be numerically postulated a priori*. In formal genetics, for example, the primary Mendelian ratios may be derived *a priori* from physical models comprising perfect shuffling procedures. Under the microscope these shuffling procedures may be observed in operation, and observed frequencies suggest that the shuffling is fairly thorough. But other statistical entities occurring in genetics, such as non-elementary recombination values, frequencies of gene penetrance, mutation rates and statistical measures of viability are less satisfactorily grounded. At best they can be referred to the unreliable model of the heavily biassed die, at worst to the investigator's ignorance of underlying mechanisms. It cannot be claimed that they are indiscriminately manipulatable by means of the probability calculus.

3. The static notion of randomness.

Current Anglo-American statistical text-books advise those wishing to select random samples to delegate the responsibility for devising and operating a randomising procedure by using one of several available published tables of random numbers. One of these (*Tippett*'s) is a collection of digits extracted from census tables; another (*Fisher* and *Yates*'s) is a similar collection from tables of logarithms; a third (*Kendall* and *Babington Smith*'s) was obtained by the use of a machine specially constructed on a principle similar to that of the roulette board. According to our requirements, none of these procedures can claim to be *approximately random*. Indeed it is difficult to see that the first two methods, since they fail to admit of indefinitely protracted application, can be regarded as procedures at all in the sense that we have used the word. But, beyond this, any merits of all three methods and of any other method which might be suggested on these terms are cancelled out by the act of selecting a section of derived numbers for publication. For (unless we take a subjective view of probability) all idea of chance must vanish when events are so far determined as to be predictable with certainty by whoever has the use of a library.

It is difficult to direct precise criticism against what constitutes so flagrant a violation of such an elementary canon. But we may note that the confusion shown by the authors referred to is, at least in part, one of aim and that in certain circumstances the compilation

of established lists of what might perhaps legitimately be called *random* numbers is possible. Attention is drawn to this confusion of aim by *Kendall*[1] in discussing his own table of random numbers:

> Thus, it is to be expected that in a table of *Random Sampling* Numbers there will occur patches which are not suitable for use by themselves. The unusual must be given a chance of occurring in its due proportion, however small. *Kendall* and *Babington Smith* attempted to deal with this problem by indicating the portions of their table (5 thousands out of 100) which it would be better to avoid in sampling experiments requiring fewer than 1000 digits.

In other words, not only should the component numbers of a random number table be produced by disorderly means, but the resulting picture should be disorderly.

These two requirements, however, are compatible only in a limiting case which in practice cannot be realised. The manner of approach to this limit is easily envisaged. We are more likely to obtain a disorderly arrangement in shuffling ten cards numbered 1, 2...10 than in shuffling three cards numbered 1, 2, 3. The notion of a disorderly arrangement, however, requires more precise definition than this.

Popper[2] considers the infinite sequence with period four commencing:

1 1 1 0 0 . . .

In this sequence the proportionate frequency of *units* is $^1/_2$: the proportionate frequencies of *units* following *zeros* and of *units* following *units* are also $^1/_2$. The sequence with period 8 commencing:

1 0 1 1 1 0 0 0 . . .

has the same properties; further, the proportionate frequencies of units following the occurrence of the pairs, 1 1, 1 0, 0 1, and 0 0 are all $^1/_2$. The sequences with periods 16 and 32 commencing:

1 0 1 1 0 0 0 0 1 1 1 1 0 1 0 0 . . .

and

0 1 1 0 0 0 1 1 1 0 1 0 1 0 0 1 0 0 0 0 0 1 0 1 1 1 1 1 0 0 1 1 . . .

similarly have proportionate frequencies of zeros unaffected by respectively three and four immediately antecedent members and

[1] Advanced Theory of Statistics. Vol. I, p. 196.

[2] See *Logik der Forschung*.

satisfy also the earlier conditions. In this way freedom from after-effect, and in consequence absence of simple periodicities, may be guaranteed up to any desired degree, and the sequences evolved become more and more disorderly in a way which suggests that they will tend in the limit to conform with some intuitive notion of randomness[1]. And indeed there exists in the limit a formal correspondence with the theory of probability which is sufficiently illustrated here by noting that the frequencies with which 4, 3, 2, 1 and 0 zeros occur in overlapping fourfold sections of the last of the sequences exhibited above are in the characteristic ratio of 1:4:6:4:1.

The chief point to be made in relation to these sequences is that, however large a claim they have to be called random, they have no relevance at all to the end we have in view. They may well have practical application. It may be useful to elaborate a system of planned disorder in experiments in which a one-to-one correspondence of response and stimulus (for example, injection of a drug and rise of blood pressure) is a valid criterion only if we exclude the possibility of delayed action or an orderly sequence of stimuli geared into a stable system of variable response. Similarly in incomplete inspection schemes where products come in linear order off a production belt, a safeguard may be required against deception arising from unsuspected periodic influences. In these cases a pre-determined disorder may be preferable to the type of disorder associated with a dynamic shuffling procedure. The latter may well provide a convenient practical method for giving *static* disorder if the number of elements to be disarranged is large and especially if the range of periodicities and aftereffects which is to be guarded against is not easily definable; but it is clear that in such a case the dynamical device is used in a purely computational capacity; the results of operating it may be legitimately adjusted in such a way as *Kendall* recommends.

On divorcing the term *random* from the notion of pure frequency and from the notion of static disorder it is possible to see more clearly the principles which must govern the elaboration of randomness for specific purposes such as we have in mind. Henceforth we shall confine our attention to the aleatory concept of randomness which requires a more precise definition than we have so far afforded it.

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[1] Thus a simple sequence is said to manifest unitary after-effect if the frequency of units following units differs from the fundamental frequency of units. Secondary and higher order after-effects are similarly defined.

4. The approximate nature of the uncertainty level in statistical experiments.

It will be easier to give this definition if we examine a simple concrete situation which the auxiliary randomising device used can be taken to rely for its validity directly on such observational foundation as the aleatory concept of randomness possesses. We introduce in the section following this an assumption which will enable us to extend the notions given here to cover more complex situations.

In the communication referred to above the writer followed the custom of nineteenth century exponents of the theory of inverse probability in regarding as typical of problems in statistical inference the assessment whether or not, on the basis of the results of repeated tossing, a coin is to be taken as having been falsely minted with its two faces identical. The example illustrates certain formal aspects of statistical experimentation but it clearly presupposes a view of randomness which cannot be justified without some qualification. We consider here a problem analogous to it but susceptible of more rigorous definition.

Suppose that I hold two counters, identical except possibly in respect of colour, one in each hand. An investigator wishes to decide between the alternatives

(*i*) ***that the counters have the same colour***

(*ii*) ***that one is black and the other white***

and is only allowed to do this by asking me to disclose the contents of one of my hands at a time at intervals during which, if I choose, I may interchange the two counters. A stochastic device is introduced, directly and naturally to resolve the problem. The investigator will seek to ensure that in every trial I reveal the contents of each hand with "probability" $^1/_2$. If he is content with a formal uncertainty level of $^1/_{16}$ he may make a firm statement following five trials, since the experiment of this extent is *a priori* adequate. The hypothesis-observation table is:

Hypotheses	*Observation* (No. of white counters observed)					
	0	1	2	3	4	5
Both counters black	**1**	—	—	—	—	—
Both counters white	—	—	—	—	—	**1**
One black, one white	1	**5**	**10**	**10**	**5**	1
	32	**32**	**32**	**32**	**32**	32

The third hypothesis is composite for, if we regard pairs of orders out of each of which one member is identical with the other except that *white* is interchanged with *black*, I may follow one of sixteen possible orders of presentation. The randomisation must be adequate relative to all of these. Similarly the *investigator* may adopt one of 16 essentially different procedures. He will aim to make all of these "equiprobable". The "probability" $1/16$ specifies the uncertainty level of the experiment. Thus the meaning we attach to the word "probable", that is to say the routine which we prescribe for the elaboration of randomness, rests in the final analysis on the nature and function of the uncertainty level.

Let us begin by using two distinguishable tetrahedral dice to obtain one of 16 putatively equiprobable events in a single joint throwing. We might suppose, even if no great attention is paid to the accuracy with which the dice are made nor to the vigour with which they are shaken, that the device will provide an approximate control over the making of false statements. How are we to ensure that this control is reliable, in the sense that the uncertainty level represents an *objective* specification of the risk associated with the adoption of a stochastic device? If no explicit instructions are given to the thrower of the dice there will be three ways in which he might subvert the structure of the experiment. He might:

(*a*) use dice heterogeneous either in respect of density or in respect of the frictional properties of surfaces and edges.
(*b*) *inspect* the initial configuration of the dice and then agitate them purposively or inadequately.
(*c*) agitate the dice inadequately, without prior inspection.

We may eliminate (*b*) by demanding that the throwing and the recording of the results of throwing should be done by different persons. To guard against (*a*) and (*c*), however, requires the *ad hoc* investigation of frequencies.

We consider first the control of what is commonly known as "bias"[1]. We associate with the *formal* uncertainty level a measure, k, of its possible inaccuracy in practice and refer to the *effective* un-

[1] It must be stressed that the word *bias* as used here does not merely denote the physical asymetry of the die. A die may be heavily biassed *physically* yet under a suitably prescribed regimen of throwing have very little *effective* bias. There is an obvious analogy with genetics. For the phenotypic manifestation of a particular chromosomal peculiarity to be adequately described a range of environments must be specified.

certainty level of the experiment under consideration as $^1/_{16} \pm k$. We seek to ensure that, given certain instructions with regard to the physical structure of the dice and the mode of throwing the proportionate frequencies of each of the 16 possible events should lie after a large number of trials within the range $^1/_{16} \pm k$. It is important to note, in view of the strictures on the notion of bias given earlier, that our claim is not to be that the proportionate frequencies should tend to a *precise limit* within the range $^1/_{16} \pm k$.

That this limitation of bias can be achieved is a matter for experimental verification. The number of trials necessary in the assessment of the relevant proportionate frequencies too should be arrived at empirically; but it is not necessary to carry a distrust of theoretical reasoning so far as to renounce the guidance it affords in this respect. If k is to be of the order $^1/_{160}$ the knowledge that, ideally,

$$\Pr\left\{ {}^1/_{16} - {}^1/_{1600} < \text{observed frequency-ratio} > {}^1/_{16} + {}^1/_{1600} \right\} = {}^{999}/_{1000}$$

if the number of trials employed is about 1,600,000 suggests that it would be advisable to make about two million trials in each individual assessment. With trials of this magnitude the effect of varying the position of the centres of gravity of dice used, keeping other circumstances as constant as possible, may be assessed. The effect of irregularities in frictional properties of edges and surfaces and of variations in method of throwing will be similarly gauged. It is reasonable to suppose that a workable routine could be recommended as a result of such an investigation.

The control of the shuffling procedure will be dealt with in a similar way. Proportionate frequencies of the sixteen possible events following the occurrence of each event should tend to lie within the $^1/_{16} \pm k$ range and it must be possible to assume that they will do so regardless of variation within the limits afforded by the specification of the vigour with which the dice are shaken.

We can, then, envisage an *empirical* standardisation of die-making and throwing which allows an objective meaning to be attached to the uncertainty level of an experiment. The experiment we have been considering, however, is the simplest stochastic experiment conceivable and is governed by an uncertainty level which would most likely in practice be regarded as inacceptably large; even so the magnitude of the preliminary investigation whose outline we have sketched is very great. In more complex situations an investigation of this type would be completely impracticable. In a comparative

trial the formal theory may require that $\binom{2n}{n}$ events, where n is of the order of 1,000, should occur with approximate equi-probability. The amount of "bias" allowable to the randomising device would then be so minute that it would be impossible in practice to establish a suitable procedure by purely empirical means.

But we have seen that the nature of shuffling procedures as ordinarily conceived is such that it seems reasonable to suppose that no more than two types of frequency need be assayed in justifying the assumption of the relevance of the probability calculus within assignable limits. Stated formally as a basic and necessary axiom this will provide all we need for fabricating randomness in the most complex situations conceivable. Moreover it will enable us to avoid almost completely the laborious investigation of frequencies we have had up to now to call for.

5. *The fundamental axiom of shuffling.*

We have noted that one of the principal objections to *von Mises*' theory is that no firm indication is given in it of the number of systems of place-selection which need be assayed in order to establish the presence of the property called randomness. There is certainly no reason why the resolution of this question should be allowed to depend either on the convenience or on the patience or on the resources of the individual investigator. But this is what often happens, even when *von Mises*' viewpoint is not explicitly accepted. If the problem of elaborating a random sequence arises—and it is most likely to do so for a somewhat ill-defined purpose—current practice requires that the investigator should choose a process which seems likely on *a priori* grounds—again ill-defined—to be irregular and then, after obtaining a fixed sequence by these means, to carry out retrospective tests of randomness on it. There exists, however, no convention which tells how many and which of, the infinite possible number of such tests should be carried out nor how extensive the experience on which the individual test is based should be. The notion of static randomness shows that in these circumstances if we were to be content with a finite number of *specified* tests we could formally use sequences derived by purely deterministic means. Any scheme which allows this consequence is manifestly ill-conceived.

We do not propose here to depart in any way from the view that probabilities should be unambiguously reflected in observable frequencies; but we shall hold that it is possible to retain this view

without accepting the tenets of *von Mises*. In order to provide a foundation for a more satisfactory frequency-theory of probability we proceed to state two fundamental principles.

Principle I: A sequence, if it is to be supposed to possess random attributes, must originate in a shuffling procedure the mechanics of whose action is observable and in which the entities shuffled are, if this is necessary, individually identifiable.

As suggested earlier this at once proscribes a large domain of application of frequency theory as at present understood; but it has this advantage that it does not entail the exclusion from investigation by formal analogy of phenomena (such as, for example, which occur in population genetics) resulting from shuffling which is known to be *imperfect*. It does not identify probability with games of chance since in games such as roulette chance enters by means of the delicacy of certain mechanisms and this is questionally related to shuffling as we understand it here.

Our second principle relates to artificially elaborated shuffling procedures. A shuffling process which ideally realises a sequence of two equiprobable events we refer to as *simple*.

Principle II: Given a well-defined simple shuffling procedure in which, within given terms of reference, neither the two fundamental frequencies nor the secondary frequencies relating to unitary after-effect can be moved outside the limits $^1{}_2 \pm \delta$*: then it may be assumed that any numerical frequencies predicted by theoretical means will actually be realised within limits obtained by supposing that the fundamental probability parameter of the sequence varies within the range* $(^1/_2 - \delta, {}^1/_2 + \delta)$.

δ is thus to be regarded as embracing *all* eccentricities of the system. That the fundamental frequencies lie in the range $\frac{1}{2} \pm \delta$ follows at once if the after-effect frequencies lie in that range; but in view of the intuitive notions to which this assumption corresponds it is convenient to draw separate attention to the two requirements. We take *Principle II* to be as necessary for the definition of probability as *Principle I*. To this extent probability is in its strictest sense definable only as it were *in the laboratory*. But this is no serious restriction since it is customary, and perhaps universally accepted, that physical entities should be so defined. It follows from our association of the probability calculus with shuffling that all probabilities are analysable in terms of equi-probability. It will therefore be sufficient to consider only shuffling procedures which are simple.

6. The interleaving of approximately random sequences.

A shuffling procedure can be most conveniently defined in relation to dice-throwing. With no more specification than the requirement that a commercially-produced die should be agitated and thrown in the usual manner it is safe to say that we can produce an approximately random sequence characterised by the parameter $^1/_2 \pm \delta$ where δ is of the order of $^1/_{10}$. This claim rests essentially on the foundation provided by the knowledge of basic frequencies which has been obtained in very wide experience of this type of phenomenon: but we could carry out, should it be thought necessary, an *ad hoc* investigation as indicated earlier. We refer to simple sequences elaborated in this way and comprising an irregular alternation of 0's and 1's as *primary stochastic sequences.*

Suppose that with defined apparatus and procedure two primary sequences are educed which happen to commence as follows:

$$1\ 1\ 1\ 0\ 1\ 0\ 0\ 1\ 1\ 0\ \ldots\ . \qquad A_1$$
$$1\ 1\ 0\ 1\ 0\ 0\ 0\ 0\ 1\ 0\ \ldots\ . \qquad B_1$$

We may derive a *secondary* sequence by changing the labelling of an event in A_1, if the event which corresponds to it in B_1 is labelled 1, leaving it unchanged if the corresponding labelling in B_1 is 0. We thus get a sequence commencing:

$$0\ 0\ 1\ 1\ 1\ 0\ 0\ 1\ 0\ 0\ \ldots\ . \qquad A_2$$

the characteristic probability parameter of secondary sequences will be specified by the range

$$\left\{ (^1/_2 + \delta)^2 + (^1/_2 - \delta)^2,\ 2(^1/_2 + \delta)(^1/_2 - \delta) \right\}$$

and we may accordingly take its value as $^1/_2 \pm 2\delta^2$. A tertiary sequence is obtainable by interleaving a primary with a secondary sequence. By the same argument its probability parameter will be specified by the range $(^1/_2 \pm 4\delta^3)$. The specification of successive sequences obtained in this way is then as follows in the table on page 55.

With so rapid a decline in error we clearly need be at no great pains to refine the initial approximation.

One feature of the above procedure is worth emphasising. If we were to begin with the assumption that the primary sequence reflects a process characterised by a probability parameter unavoidably differing from $^1/_2$ by an unknown quantity $(p - ^1/_2)$ we could develop a sequence with probability apparently *exactly* equal to $^1/_2$. For we

Sequence	*Parameter* ($\delta < 1/2$)	*Limit of Bias,* $\delta = 1/10$
A_1 (Primary)	$1/2 \pm \delta$	$1/10$
A_2 (Secondary)	$1/2 \pm 2\delta^2$	$1/50$
A_3 (Tertiary)	$1/2 \pm 4\delta^3$	$1/250$
A_4	$1/2 \pm 8\delta^4$	$1/1250$
.	.	.
.	.	.
.	.	.
A_n	$1/2 \pm 2^{n-1}\delta^n$	---

could collate two primary sequences, ignoring loci with the labelling of events identical, and taking the parallel occurrence of 1 and 0, and of 0 and 1 as our fundamental events. This follows since $p(1-p) = (1-p)p$. But this argument presupposes that numerical meaning can be attached to the concept of bias. The procedure we recommend does not employ this assumption.

7. *Randomising procedure in the comparative trial.*

The theoretical problem in designing a randomising procedure for use in a particular statistical experiment reduces to calculating the number of interleaving process needed, in terms of the degree of approximation allowed in the primary sequences employed and the accuracy required of the uncertainty level. Let us suppose we wish to carry out a sampling experiment, say a comparative trial, in which it is required to select n subjects at random from amongst $2n$. The effective uncertainty level required of the experiment we suppose to be $\varepsilon \pm \frac{\varepsilon}{k}$ and the parameter of primary auxiliary sequences used to be $1/2 \pm \delta$. We shall wish to find in terms of n, δ and k the number of primary sequences required to yield on interleaving a sequence which is adequately random.

In the general experiment of this type we should wish to make true acceptable[1] statements with theoretical probability $1 - \varepsilon$ conditional upon *some* acceptable statement being made and relative to each one of the prior hypotheses taken individually. Since it is possible for

[1] For a definition of this and other terms, see the page of the author already cited.

conditional frequencies to be proportionately more markedly deflected from their theoretical values by "bias" than straight frequencies we can more conveniently consider the special case in which the experiment is so designed that it must inevitably result in some acceptable terminal statement being made. Here the formal uncertainty level will comprise the upper bound of a set of ratios, one of which will correspond to each prior hypothesis of the experiment, that is to say one to each combination of attributes which can be possessed by the group of trial subjects. The denominator of all these ratios will be the total number of possible selections, namely $\binom{2n}{n}$; the numerator will be the number (which will be less than $\varepsilon \binom{2n}{n}$) of possibilities in a certain group of these. Accordingly, if each of the $\binom{2n}{n}$ outcomes of the sampling occurs with an effective probability within $100/k\,\%$ of its theoretical value of $1/\binom{2n}{n}$ the effective uncertainty level will be sufficiently controlled.

We may aim to make the random allocation by means of a section of a random sequence of 0's and 1's of length equal to the integer immediately above $\log_2 \binom{2n}{n}$. Let us suppose that the process we propose to use has probability-parameter $1/2 \pm \chi$.

Then if χ is chosen sufficiently small for it to happen that

$$\frac{(1/2 + \chi)^{4 \log_2 \binom{2n}{n} - \frac{1}{\binom{2n}{n}}}}{1/\binom{2n}{n}} < \frac{1}{k}$$

the uncertainty level of the experiment will be amply guaranteed.

Whence, using the approximation

$$\binom{2n}{n} = 2^{2n}/\sqrt{\pi n}$$

and, in expanding logarithmic expressions, the fact that χ is very small, we get

$$\chi = \frac{2k - 1}{2k^2 (4n - \log_2 \pi n)}$$

Thus, for example, if $k = 10$ and $n = 1{,}000$ the amount of allowable "bias" is $\frac{1}{37{,}000}$ and the conditions of the problem are certainly satisfied if we take

$$\chi \quad \frac{1}{40{,}000}$$

With δ as the measure of inaccuracy of primary random sequences, the number of mixing procedures required is

m' = smallest integer above m, where

$$(2\ \delta)^m - 2\ \chi; \qquad m \quad \frac{\log 2\ \chi}{\log 2\ \delta}$$

that is to say, we finally obtain the number of mixing procedures required as the nearest integer above

$$\frac{\log \left\{ \dfrac{2\ k - 1}{k^2\ (4n - \log_2 \pi\ n)} \right\}}{\log 2\ \delta}$$

If $\delta = {}^1/_{10}$ and k and n are as before the number of mixing procedures required is 7 (m approximately equals 6.1).

8. Conclusions – frequency and insufficient reason.

The procedure we have put forward above may at first sight appear to be unnecessarily elaborate; but it is not so compared with technical methods for indirect measurement used in other fields. It is an odd fact that those theoretical statisticians who are not unwilling to prescribe analytical procedures which must result in extensive and tedious computation, in dealing with sampling procedures allow a relaxation of commonly accepted standards of rigour, seemingly on grounds of convenience. A clue to an understanding of the situation is perhaps to be found in a passage from *Jeffreys*'s *Theory of Probability*[1].

> Most of current statistical theory, as it is stated, is made to appear to depend on one or other of various definitions of probability that claim to avoid the notion of degrees of reasonable belief. Their object is to reduce the number of postulates, a very laudable aim... My contention is that in practice no statistician ever uses a frequency definition, but that all use the notion of degree of reasonable belief, usually without even noticing that they are using it and that by using it they are contradicting the principles they have laid down at the outset.

The truth is that the procedures of all modern statistical schools which use probability theory rely on commonsense notions which if honestly systematised would yield logical calculuses formally based on some such concept as that of degree of reasonable belief. Is this circumstance a sufficient justification for the development of an explicitly subjective theory such as that of *Jeffreys* or yet for the elaboration of arbitrarily objective rules for practical procedure such as those of modern mathematical statisticians? To this we can only

[1] 2nd ed., p. 341.

answer yes if we agree that the analytical study of common modes of thought can on any terms be made profitable. In other words we must decide at the outset whether or not the investigation of the relations existing in common affairs between decisions of the individual and the incomplete knowledge on which these decisions can be said to be based can possibly result in the foundation of a valid analytical calculus. It would require a fuller discussion than is possible here to argue this matter adequately. If we chose, provisionally, to deny this possibility it will be unnecessary to enter into a detailed critique of any particular theory based on numerical measures of belief. Instead it will be useful to consider briefly the way in which the primitive notions underlying such theories can intrude into the particular practical problem with which we have been dealing. The fundamental source of confusion is the incompleteness of the investigator's knowledge. This will exist in respect both of the mechanism of the randomising device used and of the behaviour of the system to be investigated. Recognised and formalised the first requires that the criterion governing the selection of a random sample should be the guaranteeable good faith of the investigator. The matter is put clearly by Kendall in the work already cited. In discussing the problem of random sampling he writes (pp. 191–2).

> (*a*) In the first place we must require that there is no obvious connection between the method of selection and the properties under consideration. The method and the properties must be independent so far as our prior knowledge is concerned... If this matter is viewed from the standpoint of the axiomatic theory of probability the absence of knowledge about relationship between the method and the characteristic under consideration may be sufficient to ensure randomness, for the probabilities of elementary propositions then become equal—the probabilities being measures of prior attitudes of mind. But if the frequency viewpoint is adopted, it is not enough that there should be absence of knowledge of this kind, for unknown to the observer there may be relations which will prevent the elementary propositions from being true in approximately equal proportions. The presumption is that if we make as great an effort as possible to ascertain whether any relationship exists and fail to find it, there is no relationship; and hence we can assume randomness with more or less confidence. But in this approach the assumption of randomness is ultimately part of the general uncertainty of the inference from sample to population.
>
> (*b*) Secondly, we may rely on previous experience of a random method to justify its use on new occasions. This is evidently an extrapolation, and though most people would regard it as reasonable, the fact has to be realised. The axiomatic theory of probability can embrace this extrapolation within its scope, for the probabilities given by the method are assessable in terms of prior knowledge; but the frequency theory has to take the extrapolation as an additional assumption.

In both principles a form of the argument from ignorance is introduced though less obviously perhaps in (*b*) than in (*a*).

In the second case (where the ignorance is relative to the system being investigated) we have a more subtle source of confusion. In *section 4* above we considered an experiment in which there were sixteen essentially different prior hypotheses relevant to the stochastic aspect of the problem and we stated that our aim was to devise a randomising process adequate relative to each one of these. In these circumstances one aspect of the investigator's ignorance is well defined, since there would be no reason to perform the experiment if he knew with certainty which prior hypothesis was true. From this we might be led to infer that, as long as the subject of the experiment has no control over the auxiliary device used by the investigator a certain amount of carelessness is justified. For we might claim that the inadequacies of the randomising device are unlikely to gear in with the behaviour of the system under investigation. But if we try to formalise this notion we must either express the unverifiable hope that good and bad will cancel out in the long run or, acknowledging that the experiment to be performed may be the only one of its type, be led straight into the notion of equipartitioned ignorance expressed in *Bayes*' postulate.

We have sought in this paper to define *probability*, so that precise meaning can be attached to the concept of a random sample. If the axiom on which the practicability of this definition is based is to be questioned it must be questioned as if it were the postulate of a physical theory and not in relation to specific applications. Whereas *Kendall* writes (op. cit. p. 191):

> Thus a method which is random for one population may not be so for another; and even in the same population a method random for one variate may not be so for another. Randomness is relative.

We regard randomness here as *relative* only in respect of its accuracy relative to precisely defined formal ends. The uncertainty level, of a sampling experiment in its interpretation as a frequency, is only to be associated indirectly with the continuing experience of the investigator.

It may be claimed that what we have called the *aleatory* concept of probability does not get round the argument from ignorance since the shuffling of a die in a receptacle is of necessity carried on in ignorance of its successive configurations. But this depends on what we mean by ignorance. We cannot be said to be in entire ignorance

when dealing with a mechanism which in one important respect is so precisely controllable as that involved in the throwing of a die. The most important criticism, which we have purposely reserved until this stage, of *von Mises*' theory and the one which has the most grave practical implications is that it allows the probability calculus to be applied to variable phenomena which exhibit variability merely because ignorance precludes us from making the classification which would otherwise eliminate it. *Von Mises* is aware of the dangers of this possibility. At the conclusion of his book (op. cit. p. 310) he writes:

> The opinion that statistical theories are temporary explanations as compared with the final deterministic ones, which alone satisfy the craving of our mind for causality, is nothing but prejudice.

With this we are in complete agreement. Earlier however *von Mises* unequivocally includes within the domain of probability theory the actuary's study of vital statistics. We can invent any number of examples to demonstrate the incompatibility of this with the statement just cited. Any important advance in knowledge of the aetiology of disease must require an insurance company to revise its classification of prospective policy holders. That is to say, in *von Mises*' phraseology, it must recognise that sequences hitherto treated as collectives admit of the application of methods of place-selection which would reveal discrepant mortality or disease incidence ratios. Yet the possibility will have existed before the fact was disclosed. We can only conclude that in this case probability has been related to ignorance in as flagrant a fashion as in any frank application of Laplaceian principles.

Again, an example of another kind: *von Mises* regards as an empirically established collective the sequence of male and female births. It can be said however on grounds which are *not* naively empirical but which are based on known facts of reproductive physiology that our inability to predict the sex of a child prior to conception and under a wide range of conditions is largely related not to ignorance but to the effectively observable shuffling of entities with tangible substance. Any inference which might be plausibly made from statistical data is not only roughly confirmed but superseded by this knowledge since, with it, we are in a position which does not require that the shuffling procedure postulated should be theoretically perfect.

On the one hand, then, we conclude that the theory of probability

should only be invoked in circumstances where a potentially cumulative shuffling procedure is recognisable. In particular we require that the entities shuffled should admit of identification. Whether or not the shuffling is adequately thorough for the validity of a probabilistic model to be established must depend on *ad hoc* investigation.

On the other hand, we conclude that the study of frequencies in complex or inadequately comprehended situations is not facilitated by the invocation of the theory of probability. While such studies may be useful for exploratory purposes and necessary for administrative purposes, to suggest that they should serve as definitive accounts of natural phenomena is to accept the worst naiveties of the statistical sociologists of the school of *Quetelet*[1].

Summary.

Meaning can be attached to the notion of probability in relation to the study of biological phenomena only if the development of artificial random sequences can be precisely controlled.

This can be done if the basic procedure envisaged is that of shuffling. It cannot be done by means of other types of so-called chance mechanism.

Any proposed shuffling procedure is necessarily imperfect. But as a result of investigation it may be possible to assign limits to its inaccuracy.

Given approximately random sequences derived from a shuffling procedure thus controlled it is possible to obtain derivative sequences which approach more and more nearly to the ideal of perfect randomness. The closeness of the approximation is specifiable numerically.

This approach severely restricts the legitimate domain of application of probability theory. But it is possible to maintain that subjects thus excluded can be profitably discussed without the theoretical scaffolding which is customarily employed.

[1] We have made no reference to the theory of error which is historically important since a large number of applications of frequency theory are directly derived from it. The reader is referred to *N. R. Campbell*'s "Measurement and Calculation" in which the theoretical credentials of the *Gaussian* theory are vigorously attacked and the suggestion put forward that what part of the theory that is useful can and should be regarded merely as a set of convenient *ad hoc* rules for practical procedure requiring no probabilistic validification.

Résumé.

Au cours de l'étude des phénomènes biologiques il n'est possible d'attacher de l'importance à la notion de probabilité que si le développement de séries artificielles aléatoires peut être contrôlé d'une manière exacte.

Ceci devient possible si le procédé fondamental envisagé est celui de « shuffling » (mélange complet). Mais, par contre, ceci ne peut se produire s'il s'agit de n'importe quel autre type de mécanisme aléatoire.

Chaque procédé de « shuffling » envisagé est forcément imparfait. En l'essayant on peut cependant arriver à limiter son inexactitude.

Si l'on dispose de séries qui sont aléatoires d'une manière approximative et qui dérivent d'un procédé de « shuffling », contrôlé de la façon que nous venons de décrire, il est possible d'obtenir des séries dérivées qui s'approchent de plus en plus de l'idéal aléatoire parfait. On peut spécifier en chiffres l'ordre de grandeur de l'approximation.

Une telle manière de voir les choses restreint considérablement le sphère d'emploi de la théorie de probabilité. Pourtant on peut maintenir que les sujets ainsi supprimés peuvent être discutés avec profit sans l'échafaudage théorique ordinairement employée.

Zusammenfassung.

Dem Begriff der Wahrscheinlichkeit in Beziehung zum Studium biologischer Erscheinungen kann eine Bedeutung nur beigemessen werden, wenn die Entwicklung von künstlich zufälligen Serien genau kontrolliert werden kann.

Dies kann geschehen, wenn die angewandte Grundprozedur ein Mischverfahren darstellt. Hierbei ist die Zuhilfenahme jeglicher Art von sogenanntem Zufallsmechanismus unzulässig.

Jede beabsichtigte Mischprozedur ist notwendigerweise unvollkommen. Die Grenzen für ihre Ungenauigkeit dürften sich jedoch auf Grund eines Untersuchungsergebnisses bestimmen lassen.

Ausgehend von annähernd zufälligen Serien, welche von einem auf derartige Weise kontrollierten Mischprozeß abgeleitet sind, ist es möglich, abgeleitete Serien zu erhalten, welche immer näher an das Ideal der perfekten Zufälligkeit heranrücken. Die Dichte der Annäherung ist zahlenmäßig bestimmbar.

Diese Annäherung schränkt das für die Anwendung der Wahrscheinlichkeitstheorie zulässige Gebiet ernstlich ein. In diesem Zu-

sammenhange ist jedoch die Behauptung angebracht, daß Dinge, welche auf die genannte Art zum Ausschluß gelangten, auch ohne das theoretische Gerüst, welches hierbei üblicherweise verwendet wird, vorteilhaft besprochen werden können.

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ÜBER EINE MODIFIKATION DER *DAHLBERG*SCHEN METHODE ZUR SCHÄTZUNG MENSCHLICHER MUTATIONSRATEN

Von FRIEDRICH VOGEL

Dahlberg [2] hat eine Methode zur Schätzung menschlicher Mutationsraten angegeben, die auf folgender Überlegung beruht: Kenne ich den Erbgang eines Merkmales, so weiß ich, wie häufig es bei den Eltern, Geschwistern und anderen Verwandten der Merkmalsträger zu erwarten ist. Befinden sich Neumutanten unter den Merkmalsträgern, so wird in der Gesamtpopulation ein Defizit an erkrankten Verwandten auftreten. Aus diesem Defizit kann ich die Zahl der Neumutanten errechnen.

Dies ist nichts als die Verallgemeinerung der direkten Methode, wie sie von *Gunther* und *Penrose*, *Falls* und *Neel*, *Mørch* und anderen angewandt wurde, und die darin besteht, daß man – bei Dominanz – die Merkmalsträger mit zwei gesunden Eltern betrachtet, also ein Defizit an erkrankten Eltern der Berechnung zugrunde legt.

Dahlberg behandelt weiter den speziellen Fall des geschlechtsgebunden-rezessiven Erbganges und die erwartete Zahl von Merkmalsträgern unter den Großvätern der Probanden.

Relativ einfach liegen die Dinge, wenn in der Generation der Großväter keiner der Merkmalsträger sich fortpflanzen konnte. Dann kann in der Probandengeneration keiner das Gen von einem befallenen Großvater haben.

Nehmen wir an, es kämen in jeder Generation a Mutationen bei Männern, 2a Mutationen bei Frauen vor. Die das Allel tragenden Nachkommen der Frauen werden um ½ reduziert, da sie zur Hälfte männlichen Geschlechts sind. Also ist die Summe der Träger des Allels in der Deszendenz der Mütter die Summe einer geometrischen Reihe mit dem 1. Glied 2a und dem Faktor ½. Sie beträgt $\frac{2a}{1-1/2} = 4a$. Diese 4a Frauen haben 2a befallene Söhne, wozu noch die a Neumutanten unter den Söhnen selbst kommen. So ist die Gesamtzahl der Merkmalsträger:

$$G = 3a, \text{ oder } a = G/3.$$

Weiterhin analysiert *Dahlberg* den Fall, daß die Fruchtbarkeit der Merkmalsträger nicht 0 ist, sondern ein Bruchteil k des Normalen, was zur Folge hat, daß von $\frac{b}{k}$ Kranken in der Generation der Großväter mütterlicherseits nur b sich fortpflanzen[1].

Er schreibt weiter: «Unter den Müttern befinden sich doppelt so viele mit der Anlage wie unter den Männern. Also haben $\frac{2b}{k}$ Personen das Merkmal von ihrer Mutter ererbt, davon $\frac{b}{k}$ Söhne. Dazu kommen die Neumutationen in der Generation der Söhne, so daß die Gesamtzahl der Hämophilen jetzt $a + \frac{b}{k}$ beträgt. Das Verhältnis der Großväter mit dem Merkmal wird also:

$p = \frac{b}{a + \frac{b}{k}}$. Diese Gleichung ergibt, nach a aufgelöst: $a = \frac{b(k-p)}{pk}$.»

Hierbei unterliegt *Dahlberg* jedoch einem Versehen, das sich sofort darin äußert, daß er die Zahl der Merkmalsträger in der Probandengeneration mit $\frac{b}{k} + a$ angibt, während sie in der der Großväter nur $\frac{b}{k}$ beträgt; trotz der Voraussetzung des Gleichgewichtes.

[1] Es wäre besser gewesen, wenn er gesagt hätte: Von $\frac{b}{k}$ Allelen werden nur b auf die nächste Generation übertragen.

Mit anderen Worten bedeutete das: Ohne Auftreten von Neumutanten in der Generation der Probanden bliebe das Gleichgewicht zwischen Selektion und Mutation erhalten.

Die wirklichen Verhältnisse ergeben sich aus folgender Tabelle:

Tabelle 1

	Merkmalsträger:	Konduktorinnen:
1. Generation:	$\frac{b}{k}$	
2. Generation:	$\frac{b}{k}$	$b + 2a\frac{b+2a}{2} + \frac{b+2a}{4} + \ldots$ $= \frac{b+2a}{1-1/2} = 2b + 4a$
3. Generation:	$\frac{1}{2}(2b + 4a) + a$ $= b + 3a = \frac{b}{k}$	$b + 2a + \frac{1}{2}(2b + 4a) = 2b + 4a$

Es ergibt sich für die Gesamtzahl der Merkmalsträger G:

(1) $G = b + 3a$, und nach a aufgelöst:

(2) $a = {}^1/_3 (G - b)$.

Hier zeigt sich die Verwandtschaft mit der indirekten Methode von *Haldane:* Unter den Voraussetzungen einer gleichbleibenden Population und des genetischen Gleichgewichtes, die ja der ganzen Betrachtung zugrunde liegen, kann ich b durch $G \times k$ ersetzen und erhalte dann:

$$(3)\quad a = {}^1/_3 (1-k)\, G.$$

Durch Multiplikation beider Seiten mit $\frac{1}{\text{Gesamtpopulation}}$ erhalte ich die *Haldane*sche Formel:

$$u = {}^1/_3 (1 - k)x.$$

Der Unterschied ist, daß *Haldane* die Fruchtbarkeit der Probanden, *Dahlberg* das Befallensein der Großväter als bekannt voraussetzt.

Der eigene Ansatz.

*Dahlberg*s Ansatz hat den Vorteil, daß die Schätzung von k (bei *Haldane* f), die aus verschiedenen Gründen schwierig sein kann, umgangen wird. Er hat den Nachteil, daß zuverlässige Nachrichten bei 3 Generationen erforderlich sind. Da man, um menschliche Mutationsraten zu schätzen, alle Familien mit Merkmalsträgern in einer bestimmten, nicht zu kleinen Population erfassen muß, stößt dies u. U.

auf Schwierigkeiten. Es erhebt sich also die Frage, ob man den Ansatz so abändern kann, daß man mit Informationen aus einer Generation auskommt, ohne aber Aussagen über k machen zu müssen.

Zeigt das Merkmal vollständige Penetranz oder kennen wir die Manifestationswahrscheinlichkeit, so haben wir eine bestimmte Verteilung der Merkmalsträger auf die Geschwisterschaften zu erwarten. Sind Neumutanten vorhanden, so wird diese Verteilung verändert sein. Wir wissen noch mehr: Es werden nur die Geschwisterschaften mit *einem* Merkmalsträger gegenüber dem Erwartungswert vermehrt sein; in den übrigen bleibt das Verhältnis von erkrankten zu normalen Geschwistern erhalten[1]. Der Überschuß der Geschwisterschaften mit einem Kranken entspricht der Zahl der Neumutanten. Es sei:

p = Wahrscheinlichkeit für ein Kind (einen Sohn[2]), das Merkmal zu haben.
q = Deren Gegenwahrscheinlichkeit.
n = Anzahl der Kinder (Söhne) in einer Geschwisterschaft.
k_n = Anzahl der Geschwisterschaften mit n Kindern (Söhnen).
k'_n = Erwartete Anzahl von Geschwisterschaften mit n Kindern (Söhnen), wenn ich z2 (n) für z'2 (n) einsetze.
z_1 = Gefundene Anzahl von Geschwisterschaften mit einem Merkmalsträger und mindestens 2 Kindern (Söhnen).
z'_1 = Erwartete Anzahl von Geschwisterschaften mit einem Merkmalsträger und mindestens 2 Kindern (Söhnen).
z_2 = Gefundene Anzahl von Geschwisterschaften mit mehr als 1 Merkmalsträger und mindestens 2 Kindern (Söhnen).
z'_2 = Erwartete Anzahl von Geschwisterschaften mit mehr als 1 Merkmalsträger und mindestens 2 Kindern (Söhnen).
$z_2(n)$ = Gefundene Anzahl von Geschwisterschaften mit mehr als 1 Merkmalsträger und n Kindern (Söhnen).
$z'_2(n)$ = Erwartete Anzahl von Geschwisterschaften mit mehr als 1 Merkmalsträger und n Kindern.
i = Zahl der Merkmalsträger in einer Geschwisterschaft.
$r = \frac{\text{Zahl der Merkmalsträger ohne Geschwister (Brüder)}}{\text{Zahl der Merkmalsträger mit Geschwistern (Brüdern)}}$.

$$\sum_{n=2}^{\infty} z_2(n) = z_2; \quad \sum_{n=2}^{\infty} z'_2(n) = z'_2$$

Dann gilt für die erwartete Anzahl von Merkmalsträgern in den Geschwisterschaften die Binominalverteilung. Da ich nur Geschwisterschaften mit mindestens einem Merkmalsträger betrachte, gilt:

[1] Seltenheit des Merkmales vorausgesetzt, so daß wir die Neumutanten in den Geschwisterschaften, in denen das Allel schon vorhanden ist, vernachlässigen können.

[2] Wenn es sich um ein geschlechtsgebunden-rezessives Merkmal handelt.

$$z'_1 = \sum_{n=2}^{\infty} n \times \frac{p \times q^{n-1}}{1 - q^n} \times k_n$$

und:

$$z'_2 = \sum_{n=2}^{\infty} \sum_{i=2}^{\infty} \binom{n}{i} \frac{p^i \, q^{n-i}}{1 - q^n} \times k_n$$

$$z'_1 + z'_2 = \sum_{n=2}^{\infty} k_n \; .^{1})$$

Aus der bekannten $\sum_{n=2}^{\infty} k_n$ errechnet man zunächst z'_2 und prüft, z.B. mittels der χ^2-Methode, ob es mit z_2 übereinstimmt. Stimmt es nicht überein, d.h. ist $z_2 < z'_2$, so müssen sich in den z_1 Neumutanten befinden. Die wahrscheinlichste Anzahl von Neumutanten ergibt sich dann wie folgt:

$$\sum_{n=2}^{\infty} (k_n)' = \sum_{n=2}^{\infty} \frac{k_n}{z'_2 (n)} \times z_2 (n)$$

und:

$$\text{Zahl der Neumutanten } M_{(n>1)} = \sum_{n=2}^{\infty} k_n - (k_n)'$$

$M_{(n>1)}$ ist zunächst die Anzahl der Neumutanten in allen Familien mit 2 und mehr Kindern. Einzelkindern, die Merkmalsträger sind, kann man nicht ansehen, ob sie Neumutanten sind. Da man jedoch unter ihnen relativ genau so viele Neumutanten vermuten darf wie unter Personen, die Geschwister haben, fügt man der oben errechneten Zahl noch $rM_{(n>1)}$ hinzu. Es ergibt sich also:

$$(4) \quad M = M_{(n>1)} + rM_{(n>1)} \quad .$$

Bei der praktischen Anwendung kommt man in der Regel mit dem Fall $p = q = 1/2$ aus. Bei Dominanz ist:

$$(5) \quad u \text{ (Mutationsrate)} = \frac{M}{\text{Gesamtpopulation} \times 2}$$

Bei geschlechtsgebunden-rezessivem Erbgang wählt man als n die Gesamtzahl der männlichen Geschwister. Dann ist:

$$(6) \quad u = \frac{M}{\text{Gesamtpopulation der Männer}} \quad .$$

[1] Da man ja alle Familien mit Merkmalsträgern in einer großen, relativ abgeschlossenen Population erfassen muß, braucht man die Fehlerquelle der Probandenauslese nicht zu berücksichtigen.

Bei Anwendung der beiden letzten Formeln muß man allerdings, wie *Andreassen* für die indirekte Methode zeigte, eine verkürzte Lebensdauer der Merkmalsträger berücksichtigen, da dann die Zahl der an einem Stichtag lebenden Merkmalsträger keinen direkten Schluß auf die ursprüngliche Häufigkeit des Gens zuläßt. *Andreassen* fand zum Beispiel, daß die Lebensdauer der Hämophilen 1/3 der Normalen betrug; er multiplizierte also den Wert für u mit 3. Tabelle 2 gibt die Werte für $z'_2(n)/k_n$ für $p = 1/2$ und Geschwisterschaften bis zu 10 Kindern:

Tabelle 2

n:	2	3	4	5	6	7	8	9	10
$\frac{z'_2(n)}{k_n}$:	0,333	0,571	0,733	0,839	0,905	0,945	0,969	0,982	0,990

Bei $p = q = 1/2$ errechnet man $z'_2(n)/k_n$ leicht aus:

$$\frac{\text{Summe der ersten n–1 Koeffizienten der (n+1)ten Zeile des } \textit{Pascal}\text{schen Dreiecks}}{\text{Summe der ersten n Koeffizienten dieser Zeile.}}$$

An folgendem praktischen Beispiel soll das Verfahren erläutert werden: *Andreassen* publizierte ein umfangreiches Material von Hämophilen, das alle Bluterfamilien Dänemarks umfaßt. Seine Sippen enthalten insgesamt 132 Geschwisterschaften mit Hämophilen. Davon hat der Merkmalsträger bei 39 keinen Bruder. Die Verteilung der übrigen und die Anlage der Rechnung geht aus Tabelle 3 hervor:

Tabelle 3

n (Söhne)	i (Merkmalsträger)	k_n	$z'_2(n)$	$(k)_n'$	$k_n - (k_n)'$
	1 : 2 3 4 5				
2	28 : 8	36	$36 \times 0{,}333 = 12{,}0$	24,0	+12
3	15 : 8 4	27	$27 \times 0{,}517 = 15{,}4$	21,0	+ 6
4	3 : 3 2 0	8	$8 \times 0{,}733 = 5{,}9$	6,8	+ 1,2
5	3 : 3 4 0 2	12	$12 \times 0{,}839 = 10{,}1$	10,7	+ 1,3
6	1 : 2 0 0 3	6	$6 \times 0{,}905 = 5{,}4$	5,5	+ 0,5
7	0 : 0 3 0 0	3	$3 \times 0{,}945 = 2{,}8$		
8	0 : 0 0 0 1	1	$1 \times 0{,}990 = 1{,}0$		
$z_1 = 50$	$z_2 = 43$		$z'_2 =$ 52,6		21

Nun vergleiche ich zunächst z_2 mit z'_2:

$$\chi^2 = \frac{9{,}6^2}{52{,}6} + \frac{9{,}6^2}{40{,}4} = 4{,}03 \qquad p_{(m=1)} = 0{,}045 \ .$$

Der gefundene Wert ist also signifikant auf der 5 %-Stufe, und es ist sehr wahrscheinlich, daß sich unter den einzigen erkrankten Söhnen Neumutanten befinden. Unter der Annahme, die gefundenen Werte von z_2 wären gerade die Erwartungswerte, ergibt sich, wie aus Tabelle 3 ersichtlich ist:

$$M_{(n>1)} = \sum_{n=2}^{\infty} k_n - k'_n = 21$$

Nun ist noch die Zahl der Neumutanten unter den Einzelsöhnen zu ermitteln:

$$r = \frac{21 \times 39}{167} = 4{,}9 \gtrsim 5 \quad .$$

Nach (4) gilt nun:

$$M = 21 + 5 = 26.$$

Mit voller Absicht wurde das Material *Andreassen* zur Demonstration gewählt, obwohl hier die anderen Methoden für die Mutationsratenschätzung geeigneter sind. Denn *Andreassens* gut durchuntersuchte Sippentafeln erlauben schon an sich die Frage: Wieviel Fälle können höchstens als Neumutanten betrachtet werden? – Wenn man alle abzieht, deren Mütter genetisch oder blutchemisch als Konduktorinnen gekennzeichnet sind, bleiben nach unserer Zählung 18. Diese Zahl ist sehr wahrscheinlich zu hoch. Immerhin ergibt sich größenordnungsmäßig und im Rahmen der mit unserer Methode erreichbaren Genauigkeit eine befriedigende Übereinstimmung.

Wollte man hieraus nun u errechnen, so ergäbe sich ein niedrigerer Wert, als die von *Andreassen* mit der indirekten Methode errechnete und von *Haldane* [3] verbesserte Zahl. Dies erklärt sich wohl daraus, daß bei diesem Gen die Mutationsrate in den Gonaden von Männern größer ist als in denen von Frauen (*Haldane* [3]).

Die Methode ist in ihrer Anwendung fast genau so einfach, wie die indirekte und bisher beschriebene direkte Methode. Ihre Vorteile sind:

1. Vor der indirekten Methode: Es sind keine Aussagen über k nötig. Das kann wichtig sein, weil k infolge ärztlicher Therapie, eugenischer Maßnahmen, soziologischer Veränderungen usw. in wenig kontrollierter Weise schwanken kann.

2. Vor der direkten Methode: Es sind nur Informationen über eine Generation erforderlich, und es ist Anwendung bei geschlechtsgebunden-rezessivem Erbgang möglich. (Theoretisch besteht diese

Möglichkeit natürlich auch bei geschlechtsgebunden-dominantem und holandrischem Erbgang; bei autosomal-rezessivem jedoch nicht.)

Den Vorteilen stehen folgende Nachteile gegenüber:

1. Die Genauigkeit ist geringer als bei der direkten Methode, bei der ich Informationen über die Eltern habe.

2. Bei geschlechtsgebunden-rezessivem Erbgang sage ich nur etwas über die Mutationsrate in den Gonaden weiblicher Personen aus; diese aber braucht kein zutreffendes Bild über die Gesamtmutationsrate zu geben. Z.B. machte *Haldane* hier für die Hämophilie Abweichungen wahrscheinlich.

3. Es ist ein umfangreiches Beobachtungsmaterial von Geschwisterschaften mit mehreren Kindern erforderlich.

Folgende Fehlerquellen sind noch in erster Linie zu beachten:

1. Die Methode steht und fällt mit der Forderung, daß keine Phänokopien vorkommen dürfen. Das hat sie mit der sonst gebräuchlichen direkten Methode gemeinsam, während die indirekte Methode hiervon weniger betroffen ist.

2. Wenn im Extremfall immer nach der Geburt eines kranken Kindes die Fortpflanzung eingestellt wird, so gibt es in der Population nur Geschwisterschaften mit einem Merkmalsträger. Findet sich eine solche Geburtenbeschränkung nur in einem Teil der Familien, so können Neumutationen vorgetäuscht werden[1]. Besteht dieser Verdacht, so läßt sich am vorliegenden Material leicht prüfen, ob bei Familien mit einem Merkmalsträger dieser häufiger, als der Erwartung entspricht, an letzter Stelle steht.

3. Ferner kann Illegitimität Neumutationen vortäuschen.

Für eine ausführliche Diskussion der Fehlerquellen bei der Schätzung menschlicher Mutationsraten vergleiche ferner *Vogel* [4].

Zusammenfassung.

In Umbildung eines Ansatzes von *Dahlberg* wird eine Methode zur Schätzung der Mutationsrate menschlicher Gene angegeben, die auf dem Vergleich der Geschwisterschaften mit mehr als einem Merkmalsträger mit dem Erwartungswert für diese Geschwisterschaft beruht. Die Vor- und Nachteile dieser Methode im Vergleich mit den bisher bekannten sowie die Fehlerquellen bei ihrer Anwendung werden diskutiert.

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[1] Herrn Prof. Dr. *S. Koller* bin ich für den Hinweis auf diese Möglichkeit dankbar.

Résumé.

Modifiant l'idée donnée par *Dahlberg* dans une de ces conférences l'auteur indique une méthode d'estimation de la fréquence de mutations des gènes humains. Cette méthode se base sur une comparaison du nombre de personnes atteintes que l'on a constaté dans la réalité dans des fratries ayant plus d'une personne atteinte et du nombre que l'on s'attendait à obtenir. L'auteur discute les avantages et les désavantages de cette méthode en comparaison de la méthode indiquée antérieurement ainsi que les sources d'erreur qu'elle comporte.

Summary.

Modifying the method given by *Dahlberg* the author indicates another method for estimating the mutation frequency of human genes. The number of character-bearers in sibships with more than one carrier is compared with the expected number in these sibships. The advantages and disadvantages of this method compared with those of the earlier method are discussed as also the sources of error.

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ÜBER DIE VARIABILITÄT UND ERBLICHKEIT DES AKRALEN HAUTWIDERSTANDES

Von HELMUT BAITSCH

I. Einleitung und Methodik.

Carmena berichtete 1934 über die Ergebnisse von Zwillingsuntersuchungen, nach denen bei EZ der psychogalvanische Reflex (*Veraguth*) häufiger ähnlich ist als bei ZZ. Da uns weitere Untersuchungen zu diesem Thema nicht bekannt geworden sind, soll die vorliegende Untersuchung die von *Carmena* begonnenen Arbeiten, allerdings unter anderem Blickwinkel und mit veränderter Methodik, fortführen.

Die von uns gewählte *Versuchsanordnung* ähnelt im Prinzip der von *Veraguth* angegebenen: Eine Gleichspannung (2 Volt) wird über zwei nicht polarisierbare Elektroden an die Haut angelegt, mit einem Milliampèremeter wird der (scheinbare) Widerstand der Haut gemessen. Obwohl dieses Verfahren der Hautleitfähigkeitsmessung schon seit mehreren Jahrzehnten bekannt ist (*Bois-Reymond*, *Nernst*, *Rein*, *Ebbecke*), ist eine abschließende allgemeine Deutung der erhobenen Befunde noch nicht möglich. Folgende (hier nur andeutungsweise zu beschreibende) Theorie hat sich im wesentlichen durchgesetzt: Während der Dauer des Stromflusses kommt es an den Zellmembranen zu Ionenverschiebungen; so entsteht ein Potentialgefälle, das der angelegten Spannung entgegengesetzt ist. Stark gerichtete Permeabilität mit verdichteten Membranen führt zu hohen Potentialdifferenzen, der angelegte Meßstrom erscheint geschwächt. Ist die gerichtete Permeabilität mehr oder minder aufgehoben und die Membran aufgelockert, dann kommt es bei geringer Ionenstauung mit geringer Potentialdifferenz zu einem nur schwachen Gegenstrom. Da die Ionendurchlässigkeit der Zellmembranen der neurohumoralen Steuerung unterliegt (Dichtung der Membranen durch Einflüsse des Parasympathikus, Auflockerung über den Sympathikus), glaubt man in der Messung des scheinbaren Hautwiderstandes eine Methode zu besitzen, den Ablauf der vegetativen Regulationen zu verfolgen (*Regelsberger*, *Zach*, *Gratzel* und *Martin*). *Heines* unterscheidet für den so erfaßten vegetativ-nervösen Erregungsvorgang drei Anteile: «Der Grundstrom der vegetativ-nervösen Erregung bewirkt die normale Schweißsekretion und Haut-

durchfeuchtung. Diesem Grundstrom überlagern sich reflektorische Vorgänge, die von vegetativ-nervösen Perzeptionsfeldern aus angeregt werden. Sie beeinflussen weniger die effektive Schweißbildung als den jeweiligen Aktionszustand der Schweißdrüsen. Schließlich werden auch seelische Erregungen auf vegetativ nervösem Wege den Schweißdrüsen mitgeteilt. Dabei ändern sich kurzzeitig und oberflächlich die Membraneigenschaften der Zellen. Die verschiedenen Anteile des Erregungsvorganges lassen sich getrennt erfassen. Beobachtet werden jeweils die elektrophysikalischen Äquivalenterscheinungen der vegetativ-nervösen Erregung». Der bei der Messung erhaltene effektive Gleichstromwiderstand ist demnach komplexer Natur.

Der vegetative *Grundtonus* wird an den Stellen des Körpers gemessen, an denen gehäuft Schweißdrüsen vorkommen. Dieser Grundtonus (Niveau-Elektrodermatogramm n. *Regelsberger*) soll von den reflektorischen Vorgängen, die mit der Nahrungsaufnahme und dem Tag-Nacht-Rhythmus sowie den psychisch bedingten Reflexmechanismen zusammenhängen, relativ weniger beeinflußt werden; die endogen bedingten Regulationsmechanismen (speziell für die Akren wahrscheinlich vorzugsweise im Dienste einer feinen Temperaturregelung und einer optimalen Ausgangslage für die Tastempfindung) scheinen hier für eine gewisse Konstanz des individuellen Niveaus zu sorgen.

Für die *Messungen* wurde das von der Firma *Siemens-Reiniger* hergestellte Elektrodermatometer nach *Regelsberger* benutzt. Hinsichtlich der technischen Einzelheiten sei auf die dem Gerät beigegebenen Beschreibungen und die verschiedenen Publikationen zu diesem Thema verwiesen (bes. *Regelsberger*). Die Untersuchungen wurden im Anthropologischen Institut der Universität München jeweils zwischen 10 und 12 Uhr vormittags durchgeführt. Insgesamt wurden 760 Individuen gemessen. Für einen möglichst ungestörten Ablauf der Messungen wurde gesorgt, der Untersuchungsraum war normal geheizt. Jede Versuchsperson wurde vor der Messung darauf hingewiesen, daß diese nicht schmerzhaft sei und daß «es nicht elektrisiere». Dieser Hinweis scheint wichtig, um reflektorische Reaktionen im Sinne einer ängstlichen Erwartung möglichst auszuschließen. Weiter wurde darauf geachtet, daß die verwandtschaftlich zusammengehörigen Vpn möglichst innerhalb derselben kurzen Zeitspanne gemessen wurden. Mit dieser Beachtung einer hinsichtlich der rein äußeren Versuchsbedingungen möglichst gleichen Ausgangslage der zu einem Familienverband gehörigen Versuchspersonen, entsprechend der Forderung von *Kehler*, sollte die Zahl der Fehlerquellen reduziert werden. Als Meßpunkte benutzten wir die Seiten der Fingerendglieder; die Elektroden des Meßinstrumentes wurden tangential etwa an der Hautleistenendigungslinie, wie sie von *Dankmejer* und *Waltman* definiert ist, angelegt. Die Endphalangen wurden gewählt, da die vorwiegend vegetativ gesteuerte Vasomotorenreaktion hier im Bereich der relativ stärksten Kapillarisierung (*O. Müller*, *Gollwitzer-Meier*) vermutlich am deutlichsten zum Ausdruck kommt, analog dem hier sehr stark ausgeprägten «vasomotorischen Gradienten» bei thermischen Einflüssen (vgl. *Heines*).

Ob die von uns mit dem Elektrodermatometer erfaßte akrale Regulationseinstellung nur organ- oder system-spezifisch ist (d. h. nur in diesem einen Regulationsbereich anzutreffen ist, während die übrigen Bereiche andersartige Einstellungen aufweisen können) oder ob das in diesem einen Bereich festgestellte Verhalten auch für die anderen vegetativ gesteuerten Systeme gilt, die erfaßte vegetative Einstellung also individual- oder konstitutionsspezifisch ist, muß dahingestellt blei-

ben. Soweit im folgenden Gleichsetzungen und Verallgemeinerungen im zweiten Sinne gebraucht werden, möge das noch Hypothetische solcher Annahmen rückerinnert werden. Als gesichert kann es jedenfalls gelten, daß der elektrische Hautwiderstand an den Akren bis zu einem gewissen Grad ein Ausdruck ist für den momentanen Aktionszustand der Schweißdrüsen im Meßbereich und für den vegetativ gesteuerten Funktionszustand des Kapillarnetzes der Akren. Die Gleichsetzung eines hohen EDG-Niveaus mit einer relativen Sympathicotonie und umgekehrt eines tiefen Niveaus mit einer Vagotonie bleibt (vor allem bei Beachtung der Tatsache, daß sich Vagus und Sympathicus in ihrem systemhaften Zusammenhang überhaupt nicht alternativ voneinander trennen lassen) eine Arbeitshypothese (vgl. *Nesswetha*).

II. Ergebnisse.

1. Gruppenvariabilität (Verteilung der Meßwerte, Alters- und Geschlechtsunterschiede, Seitendifferenzen).

Die *Verteilung* der Meßwerte (Abb. 1, Darstellung im Wahrscheinlichkeitsnetz nach *Beckel*; Ordinatenteilung nach dem *Gauss*schen Integral, Abszissenteilung linear) entspricht mit ihrer Schiefe einer Normalverteilung 2. Art nach der Definition von *Gebelein* und *Heite*. Die Variabilität ist groß; die Variationsbreite umfaßt annähernd den ganzen Skalenbereich des Meßinstrumentes, jedoch wurden der Kurzschlußwert (67) und der Wert für den absoluten Widerstand (0) nicht beobachtet. Durch die Zusammenfassung von

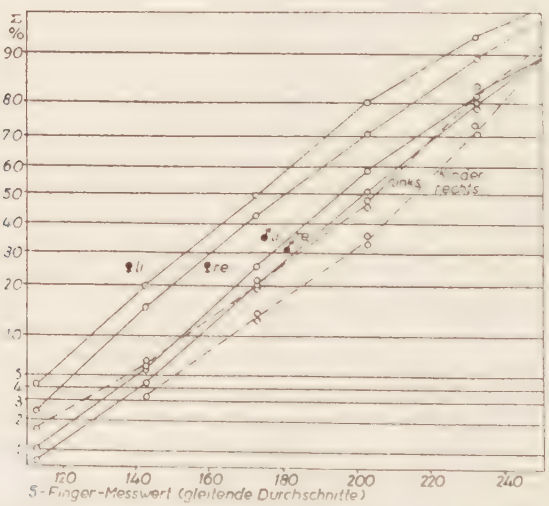

Abb. 1. Verteilung der Meßwerthäufigkeiten im Wahrscheinlichkeitsnetz (Summenprozentkurven). ♀ li, ♀ re = Frauen links und rechts; ♂ li, ♂ re = Männer links und rechts.

fünf Einzelmeßwerten für eine Seite je einer Versuchsperson haben etwaige Meßfehler für die statistische Bearbeitung weniger Gewicht. Nicht berücksichtigt werden durch diese Zusammenfassung die vorhandenen Unterschiede zwischen den einzelnen Fingern. Jedoch sind die Streuungen für die Meßwerte der zehn Finger vergleichsweise nur wenig verschieden (Tabelle 2); die Korrelation der Finger untereinander ist verhältnismässig sehr stark, bei der Prüfung des Regulationsverhaltens zeigen die Meßwerte weitgehend kongruente Schwankungen. Der Daumen zeigt in der Mehrzahl der Fälle den höchsten Meßwert, auf dem Kleinfinger findet sich häufiger der niedrigste Wert (die Unterschiede in der Verteilung der Meßwerte sind signifikant).

Die Männer haben durchschnittlich einen etwas höheren Meßwert als die Frauen (Tabelle 1), die Kinder zeigen (ohne wesentlichen Geschlechtsunterschied) ebenfalls durchschnittlich höhere Meßwerte als die Mütter. In allen Altersgruppen und in beiden Geschlechtern sind Rechts-Links-Unterschiede vorhanden: *Durchschnittlich* finden sich rechts etwas höhere Meßwerte als links.

Tabelle 1. Mittelwerte des akralen EDG bei Erwachsenen und Kindern, nach Seite und Geschlecht getrennt.

	Seite	n	M	σM	σ	V
Männer	rechts	200	217.18	2.56	36.14	96–308
	links		212.05	2.64	37.19	107–299
Frauen	rechts	120	197.42	3.57	39.12	108–298
	links		189.16	3.44	37.65	93–276
Jungen	rechts	63	225.85	4.02	31.91	143–294
	links		215.79	4.37	34.67	125–293
Mädchen	rechts	50	226.60	4.97	35.14	144–299
	links		217.90	4.93	34.90	146–282

2. Individuelle Variabilität.

a) Bei fünf weiblichen Versuchspersonen im Alter von 27–45 Jahren wurden in der Zeit vom 20.7.–15.8.1953 insgesamt 850 Einzelmessungen durchgeführt. Die Mittelwerte und Streuungen sind in Tabelle 2 dargestellt. Da den Versuchspersonen keinerlei Einschränkungen hinsichtlich der Aufnahme von Genußmitteln (Nikotin und Kaffee) auferlegt waren, die Messungen weiterhin nicht nur

Tabelle 2. Mittelwerte und Streuung der EDG-Meßwerte bei 5 Versuchspersonen, berechnet aus 17 Messungen je Finger, Versuchsdauer 4 Wochen. Im 2. Teil der Tabelle finden sich die Meßwerte der gleichen Versuchspersonen, abgenommen 4 Monate vor der Meßserie im 1. Teil der Tabelle.

		Rechts					Links				
VP		Dig. 1	Dig. 2	Dig. 3	Dig. 4	Dig. 5	Dig. 1	Dig. 2	Dig. 3	Dig. 4	Dig. 5
ES.	M	40.41	35.29	34.53	35.41	33.35	39.59	35.06	34.76	34.64	34.05
	σ	2.816	2.912	3.204	3.083	3.181	2.676	2.210	2.413	2.452	2.690
BB.	M	37.47	34.47	32.35	34.94	35.23	39.94	34.59	31.88	31.41	33.76
	σ	2.057	2.026	3.200	3.039	2.507	3.244	2.641	4.310	3.306	2.389
AG.	M	40.65	36.35	33.53	34.82	35.47	38.82	35.71	32.94	34.65	33.18
	σ	2.656	2.498	2.355	3.034	3.612	3.294	2.444	3.634	2.700	3.232
SL.	M	34.53	31.18	31.29	31.12	30.06	33.71	32.47	31.35	30.47	30.24
	σ	3.238	3.729	3.981	3.012	2.960	2.934	3.392	3.049	3.008	2.999
MK.	M	34.71	32.18	31.59	31.71	29.76	34.53	32.41	30.06	30.24	26.76
	σ	6.693	7.119	7.507	7.579	6.198	5.259	6.747	6.813	7.642	5.281
ES.	6. 2.	38	32	32	35	34	41	36	34	33	31
BB.		39	32	31	34	34	37	30	30	33	34
AG.		35	32	28	29	30	35	31	32	27	30
SL.		37	34	34	32	31	36	35	34	31	30

am Vormittag, sondern teilweise auch am frühen und am späten Nachmittag durchgeführt wurden sowie auf vorherige Nahrungsaufnahme nicht geachtet wurde, erscheint die beobachtete Streuung der Meßwerte relativ gering. Hinzu kommt, daß die Versuchspersonen Frauen sind (dabei eine Graviditas mens III–IV), also stärkere zyklusbedingte bzw. allgemein hormonell ausgelöste Reaktionen im Endstromgebiet der Akren angenommen werden müssen. Die VP M.K. weicht deutlicher mit einer größeren Streuung von den übrigen vier VP ab. Wir führen diese größere Streuung darauf zurück, daß diese VP, die zudem eine starke Raucherin ist, gelegentlich im Anschluß an Laborarbeiten mit kaltem Wasser (VP ist Fotolaborantin) gemessen wurde (vgl. Abb. 2); möglicherweise hat das Bestehen einer chronischen Otitis media bei dieser Versuchsperson ebenfalls einen Einfluß auf die Meßwerte (erworbene angiopathische Reaktionslage bei rezidivierenden Infekten, *Ratschow*). Die mit den Meßergebnissen dieser Versuchsgruppe durchgeführte Varianzanalyse zeigt, daß die Streuung «zwischen der Person» vergleichsweise die größte ist, das Vorliegen konstitutioneller (individueller) Unterschiedlichkeiten im akralen EDG erscheint so gesichert. Die Varianz «zwischen den Tagen» ist dagegen erheblich geringer, sie ähnelt größenordnungsmäßig etwa der Varianz «zwischen den Seiten innerhalb der Personen und Tage».

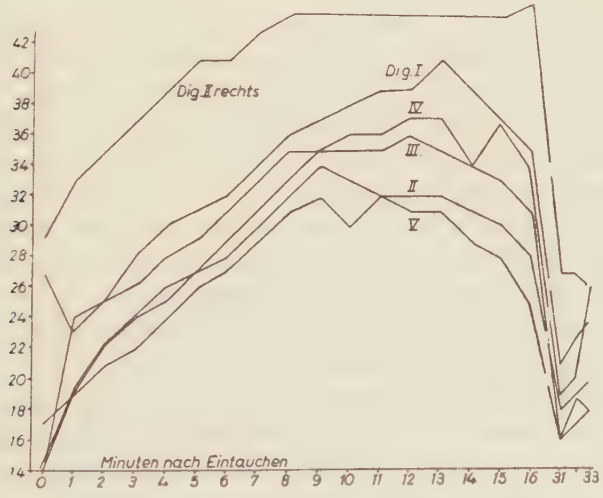

Abb. 2. Akrales Dermatogramm der linken Hand nach Eintauchen der rechten Hand in kaltes Wasser (10°C). Dauer des Eintauchens 3 Minuten. Beginn der Messung nach dem Herausnehmen der Hand aus dem Wasser. (Versuchsperson MK; vgl. Tabelle 2.)

Die ausführliche Darstellung dieser mehrgliedrigen Streuungszerlegung erfolgt an anderer Stelle gemeinsam mit *Bauer*.

b) Bei über mehrere Stunden fortlaufend durchgeführten Messungen zeigen sich geringe Schwankungen zwischen den einzelnen Meßwerten, die durchschnittliche Differenz zwischen je zwei aufeinanderfolgenden Messungen ist bei den beiden untersuchten VP nur gering (Tabelle 3).

Tabelle 3. Durchschnittliche Differenz der Meßwerte je 2 aufeinanderfolgender Messungen bei 670 Messungen innerhalb eines Zeitraumes von 3 Stunden.

	Rechts					Links				
	I	II	III	IV	V	I	II	III	IV	V
VP 1	2.10	1.37	1.73	2.39	1.73	2.19	1.67	1.81	2.45	2.15
VP 2	2.03	2.50	2.34	2.03	2.03	1.71	2.39	1.37	1.68	1.71

c) Eine im Dermatom Th1 (ulnares Drittel des Handrückens) mit Nonylsäurevanillylamid (rechts) bzw. Nikotinsäure-Butoxyaethyl-Ester (links)[1] erzeugte starke Hyperämie führte bei einer VP nach einer rechts längeren und links kürzeren Latenzzeit zuerst zu einer geringen Senkung und dann zu einer stärkeren Hebung der EDG-Werte, nach einigen Nachschwankungen bewegte sich das Niveau wieder zur individuellen Norm hin. Diese regulativen Vorgänge entsprechen den für vegetative Steuerungen typischen periodisch gedämpften Ausschwingungsvorgängen. Zwischen den zehn Fingern jeder Versuchsperson bestehen starke Korrelationen in diesem Regulationsgeschehen. In der Ansprechbarkeit auf die beiden verwendeten Hautreizmittel bestehen individuelle Unterschiede; das Regulationsverhalten der einzelnen Individuen ist wechselnd nach der Höhe des Regelausschlages und nach der Regeldauer. Es findet sich also m.a.W. eine individuell (konstitutionell) unterschiedliche Regelgüte (zur Definition der verschiedenen Komponenten des Regelgeschehens vgl. *Drischel*). (Vgl. hierzu auch Abb. 2.)

d) Daß die Akren im Regulationsgeschehen offenbar eine gewisse Sonderstellung in dem Sinne einnehmen, daß hier im Gegensatz zu anderen Bezirken der Haut ein einigermaßen konstantes

[1] Der Firma Dr. Karl Thomae, die uns liebenswürdigerweise die verwendeten Chemikalien zur Verfügung stellte, verdanken wir den Hinweis, daß die unterschiedlich langen Latenzzeiten von der biochemischen Eigenart der beiden Stoffe herrühren.

EDG-Niveau gehalten wird, zeigt folgender Versuch: Eine VP wurde extremen Temperaturgegensätzen ausgesetzt (Saunabad mit Lufttemperatur von 90° Celsius). Von den Dig. II und III der linken Hand dieser VP sind die End- und Mittelglieder amputiert. Wie Tabelle 4 erkennen läßt, zeigen diese Finger sehr viel größere EDG-Schwankungen als die gesunden Finger. Regeltheoretisch ausgedrückt besagen diese Befunde, daß an den gesunden Fingern die Regeltätigkeit optimal ist, denn die Regelfläche (von der Regelkurve begrenzte Fläche) ist klein. Bei den amputierten Fingern hat man dagegen den Eindruck, als ob die Amplitude der periodischen Schwankung größer geworden sei, eine optimale Dämpfung bis zur schnellen Wiederherstellung der Ausgangslage fehlt also (periodisch «entarteter» Regeltypus, *Drischel*).

Tabelle 4. Akrales EDG bei Einwirkung starker Temperaturunterschiede auf die VP (Saunabad).

	Rechts					Links				
	I	II	III	IV	V	I	II[1]	III[1]	IV	V
Ruhewerte	48	45	43	42	38	47	*32*	*36*	43	39
nach 10' Sauna . . . . (Lufttemperatur 90° C)	53	51	48	49	45	55	*42*	*46*	50	46
nach 13' Abkühlung in Wasser	47	44	42	39	40	45	*33*	*39*	44	42
nach 10' Ruhe	46	43	39	36	37	45	*16*	*26*	42	41
2. Saunagang (10') . . .	49	47	43	42	41	48	*37*	*43*	45	43

[1] Dig. II und III Mittelglied und Endglied amputiert; Dig. II mehrfach wegen Phantomschmerzen nachoperiert. Messung seitlich am Amputationsstumpf.

e) Sämtliche VP wurden daraufhin befragt, ob sie Raucher oder Nichtraucher sind. Für eine unausgelesene Untersuchungsreihe von 272 Männern ergibt sich daraufhin das in Abb. 3 dargestellte Ergebnis: Bei den Rauchern sind die EDG-Meßwerte durchschnittlich höher als bei den Nichtrauchern. Wesentlicher als diese Erhöhung des Mittelwertes erscheint der Verteilungsunterschied: bei den Rauchern finden sich auf Kosten der Klassen mit niedrigen und mittelhohen Meßwerten vor allem die Klassen mit hohen Meßwerten stark besetzt. Die größere Streuung der Meßwerte bei den Rauchern wirkt sich also vorzugsweise nur nach einer Seite, nämlich zu den hohen Meßwerten hin, aus. Da nur ein Teil der Raucher diese starke Erhöhung der Meßwerte zeigt, liegen bei unseren VP offenbar konstitutionelle Unterschiede in der Nikotinwirkung vor.

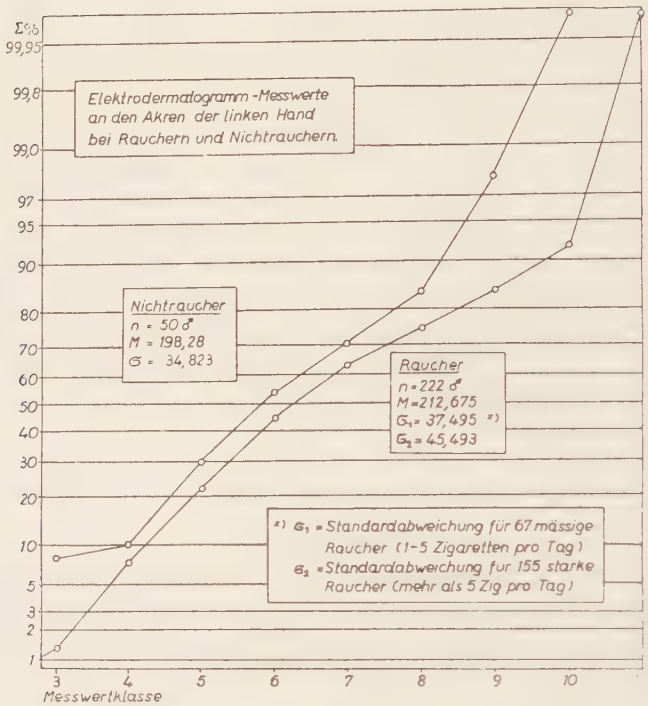

Abb. 3.

Die Streuungsanalyse ergibt ein $Q = 2{,}76106 < P = 0{,}05/2{,}99$. Der daraufhin durchgeführte Mittelwertvergleich (t = Test) n. *R. A. Fisher* führt zu $t_{1,3} = 2{,}268 > P = 0{,}05/1{,}97 < P = 0{,}01/2{,}60$. D.h. die Differenz der Mittelwerte von Nichtrauchern (Gruppe 1) und starken Rauchern (3) ist mit einem P zwischen 0,05 und 0,01 gesichert. Der Vergleich der Verteilungen ergibt (bei günstigster Klassenbildung) ein $\chi^2 = 8{,}77$ bei 2 Freiheitsgraden ($< P = 0{,}01/9.210$; $> P = 0{,}02/7{,}824$).

3. Erblichkeitsuntersuchungen.

Da der Hautwiderstand sich, statistisch gesehen, als ein abstufbares quantitatives Merkmal darstellt, liegt es nahe, die erblichen Beziehungen als Elter-Kind-Korrelation zu erfassen. Es wurden hierzu für die Mutter-Kind-Verbindungen (die alle als abstammungsmäßig sicher angenommen werden können) und die mutmaßlichen Vater-Kind-Verbindungen Korrelationstafeln aufgestellt.

Soweit es sich um Fälle aus erbbiologischen Vaterschaftsuntersuchungen handelte, wurden nur die Fälle herangezogen, in denen ein Mann mit «an Sicherheit grenzender Wahrscheinlichkeit» als Vater festgestellt wurde. Ergänzend zu diesen Fällen kamen mehrere Familien aus dem engeren Kreis der Institutsangehörigen. Für die Mittelwertberechnung und die Aufstellung der Verteilungen wurden weiter

eine größere Zahl von Studenten und Institutsangehörigen sowie Männer, Frauen und Kinder aus dem Bekanntenkreis des Verfassers untersucht. Alle VP waren gesund oder (in einigen wenigen Ausnahmefällen) zumindest nicht ernstlich erkrankt. Nicht in die Bearbeitung einbezogen wurden die VP, bei denen Fingerverstümmelungen oder auch schon mäßige Narbenbildungen vorlagen, da der Meßwert im Bereich der Narben meist niedriger ist als im gesunden Bereich.

Die Korrelationstafeln lassen erkennen, daß extrem große Elter-Kind-Differenzen seltener auftreten als bei zufälliger Verteilung zu erwarten wäre. Eltern mit niedrigen Meßwerten haben selten Kinder mit hohen Meßwerten: den Eltern mit hohen Meßwerten lassen sich zwar Kinder mit niedrigen Meßwerten zuordnen, jedoch sind sie nicht so häufig, wie es bei zufälliger Verteilung zu erwarten wäre.

Tabelle 5. Elter-Kind-Korrelationen.

Mütter-Kinder	rechts	+0.5477	182 Paare
	links	0.3307	183 Paare
Väter-Kinder	rechts	0.0483	130 Paare
	links	0.1007	128 Paare

Für die Elter-Kind-Korrelationen ergeben sich die in Tabelle 5 dargestellten Koeffizienten. Die Korrelationen sind für die Mutter-Kind-Verbindungen signifikant; die Vater-Kind-Korrelation ist nicht gesichert positiv. Die im Vergleich zu den Vater-Kind-Korrelationen stärkere Mutter-Kind-Korrelation führen wir darauf zurück, daß in unserem Untersuchungsgut die Kinder in ihren Lebensbedingungen mehr ihren Müttern angepaßt sind als den Vätern, die meist aus einer anderen Umwelt mit anderen Lebensbedingungen stammen. Die schwächere Vater-Kind-Korrelation rührt, was die Besetzung der Korrelationstafel betrifft, in der Hauptsache daher, daß Väter mit extrem hohen Meßwerten nicht selten Kinder mit extrem niedrigen Meßwerten besitzen. Hierdurch wird die im allgemeinen in Richtung einer linearen Korrelation aufgegliederte Korrelationstafel im Quadranten «hohe Meßwerte bei Vätern – niedrige Meßwerte bei Kindern» nicht mehr linear. Bei den Mutter-Kind-Kombinationen findet sich diese Störung nicht so stark ausgeprägt. Die Erklärung, daß dieser Effekt allein auf der Dominanz der hohen Meßwerte gegenüber den niedrigeren beruhe, verliert so an Gewicht gegenüber der Annahme, daß bei den Männern mehr als bei den Frauen zusätzliche Umwelteinflüsse (die fast regelmäßig zu einer Erhöhung und nicht zu einer Erniedrigung der EDG-Meßwerte führen) sich auswirken. Diese Deutung ge-

winnt an Wahrscheinlichkeit, wenn man berücksichtigt, daß die störenden Meßwertklassen 10 und 11 (5-Fingerwert über 280) außerhalb des statistischen Normbereichs ($M \pm 1{,}96\ \sigma$, *H. Günther*) liegen, hier also pathologische oder extrem exogen beeinflußte Konstitutionsvarianten vorliegen können. (An die Zusammenhänge zwischen der Hautleitfähigkeit und dem Nikotingenuß wird erinnert!) Da diese pathologisch zu wertenden Varianten sich speziell an den Rändern der Korrelationstafeln auswirken müssen, können schon wenige Fälle den Korrelationskoeffizienten stark beeinflussen. Einen besseren Eindruck vom Grad des Elter-Kind-Zusammenhanges geben hier die Regressionen bzw. die Entsprechungstabellen (Tabelle 6): Die arithmetischen Mittel der Kindergruppen, bezogen auf bestimmte Elterklassen, zeigen in allen Elter-Kind-Kombinationen eine ansteigende Tendenz, ausgenommen die Kinder der Eltern mit der Meßklasse 10 und 11 (Väter) bzw. 9 (Mütter).

Tabelle 6. Arithmetisches Mittel der EDG-Meßwerte der Kinder aus Mutter-Kind- und Vater-Kind-Kombinationen (rechts).

Meßwertklasse des Elters[1]	Kinder aus Vater-Kind-Kombination		Kinder aus Mutter-Kind-Kombination	
	n	M	n	M
1	5	201.40	4	179.25
2				
3			5	184.20
4			21	189.95
5	12	211.75	42	214.07
6	31	213.74	29	225.41
7	35	224.74	43	230.98
8	20	229.15	19	232.32
9	12	234.08	7	220.85
10	16	209.74	6	236.83
11			7	247.28

[1] Klasseneinteilung nach Tabelle 7.

Für die *Familienuntersuchung* wurden aus dem Gesamtuntersuchungsgut alle vollständigen Vater-Mutter-Kind-Kombinationen zusammengestellt. Insgesamt konnten so 114 Familien mit 120 Kindern gebildet werden. Anhand des Schemas in Tabelle 7 wurden Meßwertklassen eingeteilt, die Kombinationsmöglichkeiten der so aufgestellten Elternklassen ergeben sich aus der ersten Spalte der Tabelle 8 und 9.

Die Verteilung der Kinder auf diese verschiedenen Elternkombinationen läßt eine Tendenz dahingehend erkennen, daß Eltern mit

Tabelle 7. Klasseneinteilung der 5-Finger-Meßwerte des akralen Elektrodermatogramms.

EDG-Werte	Klassennummer
bis 100	1
101–120	2
121–140	3
141–160	4
161–180	5
181–200	6
201–220	7
221–240	8
241–260	9
261–280	10
über 281	11

Tabelle 8. Akrales EDG bei Kindern und ihren Eltern (rechts).

Typen der Elternkreuzung	Zahl der Elternpaare	Meßwertklasse der Kinder[1]								
		3	4	5	6	7	8	9	10	11
1–4:1–4	1	—	1	—	—	—	—	—	—	—
1–4:5–6	10	1	—	—	4	5	—	—	—	—
1–4:7–11	11	—	—	4	—	4	1	2	—	—
5–6:5–6	10	—	—	2	1	1	2	2	1	—
5–6:7–11	48	—	1	1	9	10	18	11	3	1
7–11:7–11	34	—	2	3	1	3	11	7	4	4

[1] Klasseneinteilung siehe Tabelle 7.

Tabelle 9. Mittelwert der EDG-Meßwerte bei den Kindern verschiedener Elternkreuzungen (Einteilung Tabelle 7).

Typen der Elternkreuzung	Mittelwerte der Kinder			
	n	Rechts	n	Links
1–4:1–4	1	150.00	2	171.00
1–4:5–6	10	189.10	12	191.66
1–4:7–11	11	201.27	19	205.89
5–6:5–6	9	221.10	21	208.14
5–6:7–11	54	223.55	41	205.49
7–11:7–11	35	233.08	25	228.32

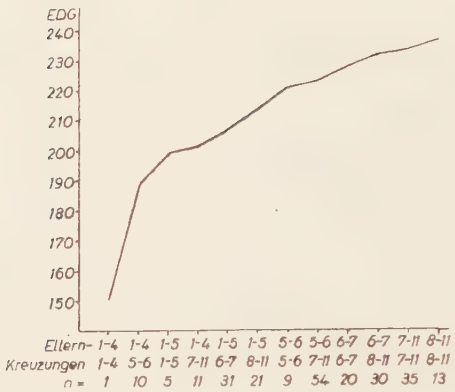

Abb. 4. Arithmetische Mittel der 5-Finger-Meßwerte (rechts) von Kindern verschiedener Elternkreuzungen. Klassenbildung bei den Elternkreuzungen nach der Einteilung Tabelle 7. Gesamtzahl der Elternpaare = 115; Gesamtzahl der Kinder = 120.

durchschnittlich niedrigen Meßwerten bevorzugt Kinder mit ebenfalls niedrigen Meßwerten haben. So kommen in den Eltern-Kombinationen 1–4:1–4 und 1–4:5–6 Kinder mit hohen Meßwerten überhaupt nicht vor. Dagegen finden sich unter den Kindern der Elternkombinationen mit hohen Meßwerten neben relativ vielen mit ebenfalls höheren Meßwerten auch solche mit niedrigeren. Man erhält so den Eindruck, als ob die hohen Meßwerte dominant seien gegenüber den niedrigen, wobei die Dominanz abgestuft erscheint. In der graphischen Darstellung (Abb. 4) sind die möglichen Elternkombinationen, in verschiedener Einteilung und Gruppierung, auf der Abszisse abgetragen; auf der Ordinate findet sich der Maßstab für die arithmetischen Mittel der EDG-Meßwerte der Kinder aus den jeweiligen Elternkreuzungen.

Tabelle 10. Prüfung der in Tabelle 8 und 9 getroffenen Gruppierung auf Signifikanz der Verteilungsunterschiede mittels der Streuungszerlegung (Varianzanalyse *R. A. Fisher*).

Art der Variation	Zahl der Freiheitsgrade	Summe der Abstandsquadrate	Streuung
Zwischen den Gruppen	4[1]	23,556·24	5,889·06
Innerhalb der Gruppen	115	108,517·89	943·63
Insgesamt	119	132,074·13	...

$Q = 6.24 > 3.479\ (P = 0.01) > 4.947\ (P = 0.001)$.

[1] Wegen der geringen Besetzung der Elterngruppe 1–4:1–4 wurde für die Durchführung der Varianzanalyse diese Gruppe zusammengelegt mit der Elterngruppe 1–4:5–6, sodaß insgesamt 5 Gruppen gebildet waren; hierdurch ergibt sich für die Variation «Zwischen den Gruppen» die Zahl der Freiheitsgrade 4.

Die Varianzanalyse (*R. A. Fisher*) gibt für die Verteilung der Kindermeßwerte (rechte Hand) auf die verschiedenen Elternkreuzungen einen signifikanten Wert für Q; d. h. es ist damit als erwiesen anzusehen, daß die beobachteten Unterschiede in der Verteilung nicht mehr zufällig sind (Tabelle 10).

Da in der vorstehend beschriebenen Aufgliederung des Materials zur Klassenbildung jeweils die 5 Meßwerte einer Hand in einen Wert zusammengefaßt wurden, bleiben die etwa möglichen Erbeinflüsse in der Verteilung der Meßwerte auf die einzelnen Finger sowie in der Asymmetrie unberücksichtigt. Daß hier Erbeinflüsse wirksam sind, fiel bei der Durchsicht des Materials immer wieder auf. So erscheint die Übereinstimmung in der Verteilung der Meßwerte und die Ähnlichkeit in der geringen Asymmetrie bei den Meßwerten zweier Brüder deutlich (Tabelle 11).

Tabelle 11. Verteilung der EDG-Meßwerte bei 2 Brüdern.

Dig.	rechts I	II	III	IV	V	Σ	links I	II	III	IV	V	Σ
F.S. (Prob. Nr. 17a)	48	48	45	41	42	*224*	43	41	41	39	35	*199*
K.S. (Prob. Nr. 17b)	49	49	43	41	39	*221*	41	44	37[1]	36	37	*195*

[1] Große Narbe am Fingerendglied.

In einer der beobachteten Familien fanden sich die in der Tabelle 12 dargestellten Meßwerte. Während die Verteilung der Meßwerte auf die einzelnen Finger des Kindes wie eine Kombination aus den Verteilungen der beiden Eltern erscheint, finden sich in den 5-Finger-Werten auffallende Vater-Kind-Ähnlichkeiten sowohl nach der absoluten Höhe als auch nach der Asymmetrie. Diese Familie ist in unserem Untersuchungsgut die einzige, in der beide Eltern deutlicher asymmetrisch sind. Die Tatsache, daß das aus dieser Verbindung hervorgegangene Kind ebenfalls eine ausgeprägte Rechts-Links-Asymmetrie zeigt, läßt vermuten, daß die starke Asymmetrie rezessiv ist gegenüber der Symmetrie.

Tabelle 12. Verteilung der Meßwerte auf die 10 Finger bei einer Familie[1] mit starken Asymmetrieerscheinungen im EDG.

Dig.	rechts I	II	III	IV	V	Σ I–V	links I	II	III	IV	V	Σ I–V
Vater	44	40	42	42	36	*204*	34	33	32	28	31	*158*
Kind	59	52	35	32	28	*206*	35	29	29	28	30	*151*
Mutter	38	31	36	31	24	*160*	45	41	37	33	28	*184*

[1] Fall Nr. 109; Prob. Nr. 413, 414, 416.

Tabelle 13 zeigt die verschiedenen beobachteten Eltern-Kind-Kombinationen. Nach der Tabelle 15 erscheint es möglich, daß der rezessive Faktor für die Asymmetrie nicht quantitativ abgestuft ist, denn die arithmetischen Mittel der Asym-

metriewerte bei den Kindern, bezogen auf abgestufte Asymmetrieklassen der Eltern, steigen nicht stetig sondern sprunghaft an: Die Grenze zwischen Symmetrie und Asymmetrie könnte danach etwa zwischen 30 und 35 Meßwerteinheiten (Seitendifferenz der 5-Finger-Meßwerte) liegen; dieser Wert entspricht etwa gerade der Streuungseinheit σ.

Tabelle 13. Auftreten von Asymmetrie bei Kindern verschiedener Elternkreuzungen

Elternkreuzungen	Kinder symmetrisch – mäßig asymmetrisch	Kinder asymmetrisch – stark asymmetrisch
symmetrisch : symmetrisch		
leicht asymmetrisch : symmetrisch		
leicht asymmetrisch : leicht asymmetrisch	116	3
mäßig asymmetrisch : symmetrisch		
mäßig asymmetrisch : leicht asymmetrisch		
stark asymmetrisch : leicht asymmetrisch	—	1

Tabelle 14. Einteilung der Asymmetriegrade.

Rechts-Links-Differenz in Meßwertklassen	Asymmetriegrad
0	symmetrisch
1	leicht asymmetrisch
2	mäßig asymmetrisch
3	asymmetrisch
4	stark asymmetrisch

Tabelle 15. Mittelwerte der Rechts-Links-Differenzen bei Kindern, bezogen auf die Symmetrieverhältnisse eines Elters.

Rechts-Links-Differenz bei dem Elter	n	Mittelwerte bei den Kindern
0– 3	50	14.28
4– 7	42	13.62
8–11	38	13.32
12–15	31	15.77
16–19	30	14.87
20–23	14	12.64
24–27	9	16.33
28–31	11	12.63
32–35	3	23.33
36–39	5	19.40
40–x	8	21.13

III. Besprechung der Ergebnisse.

Das akrale EDG zeigt eine große *Variationsbreite:* Es gibt Individuen mit hohen und solche mit niedrigen Meßwerten, eine größere Gruppe besitzt mittelhohe EDG-Meßwerte.

Die *Asymmetrieerscheinungen* in der Leitfähigkeit der Haut wurden u. W. bisher noch nicht planmäßig untersucht. Die Ergebnisse unserer Untersuchungen lassen sich vereinfachend dahingehend zusammenfassen, daß die rechte Seite durchschnittlich etwas mehr ergotrop (relativ sympathikusbetont) charakterisiert erscheint als die linke (relativ mehr trophotrop, vagusbetont). Dieser Befund hat Parallelen in der Asymmetrie des Nagelwachstums und in der Pathologie der efferenten vegetativen Fasern: An der rechten Hand findet sich ein durchschnittlich stärkeres Nagelwachstum als an der linken (*Pradier, Knobloch, Wiegand, Voit* u. a.); Reizerscheinungen an den efferenten vegetativen Fasern äußern sich u. a. in Hyperhidrosis, Hypertrichosis und in gesteigertem Nagelwachstum, während Ausfallserscheinungen u. a. zu Hypo- und Anhydrosis sowie zu Cyanose und Hyperkeratose führen (zit. n. *Gagel*). Bei einseitiger Endangiitis obliterans der unteren Extremitäten zeigt der kranke Fuß oft keinerlei Schweißbildung mehr, während der gesunde noch stark transpiriert (*Ratschow*). Es erscheint möglich, daß diesen Parallelen tiefere kausale Zusammenhänge zugrundeliegen. Asymmetrieen in verschiedenen anderen vegetativ gesteuerten Funktionen wurden an der oberen Extremität mehrfach beobachtet (Blutdruck: *Beckmann, Randig* und Mitarbeiter; Grad der Wärmeabgabe: *Stewart;* Hauttemperatur: *Freeman, Pfleiderer, Zselyonka;* Volumenschwankungen: *Danielopolu* und *Carniol;* Unterschiede in der Durchblutung: *Aschoff, J.*). *Grodzicki* deutet die funktionellen Korrelate morphologischer Asymmetrien beim Menschen im Sinne der Lehren von *Ricker, Scheidt, Speransky.*

Reizvolle Zusammenhänge lassen sich hier zwischen vegetativem System, EDG und Tastleistensystem vermuten: Bei beiden Geschlechtern fast aller bisher untersuchten Populationen finden sich im Tastleistensystem links durchschnittlich etwas mehr «primitive» Mustertypen als rechts; beim männlichen Geschlecht sind analog die progressiven (phylogenetisch vermutlich jüngeren) Musterformen etwas häufiger als im weiblichen Geschlecht. Da die systematische Anordnung der Tastleisten auf den Fingerbeeren letztlich als das Ergebnis funktioneller, entscheidend vom Gefäß-Nerven-Apparat der Akren abhängiger Vorgänge anzusehen ist (*Bonnevie*), erscheint die Annahme naheliegend, daß auch das vegetative System ursächlich in die Entwicklungsphysiologie des Tastleistensystems hineinspielt. Die Asymmetrieerscheinungen im Tastleistensystem und im EDG, die sowohl nach ihrer Richtung

als auch nach ihrer quantitativen Ausprägung sich ähnlich sind, könnten so als der Ausdruck eines durchschnittlichen relativen Überwiegens der sympathischen (phylogenetisch jüngeren) Anteile des vegetativen Systems auf der rechten Seite gedeutet werden. *E. Fischer* hatte schon früher auf die Möglichkeit engerer Zusammenhänge zwischen Tastleistensystem und Nervensystem (speziell in seinen segmentären Beziehungen) hingewiesen; Andeutungen hierzu finden sich schon bei *Bonnevie*, neuere Theorien zu diesem Problem entwickelte *W. Scheidt*.

Da die von uns angewandte Methodik nur einen stichprobenhaften Querschnitt durch das regulative Geschehen gibt, ist eine exakte Aussage darüber nicht möglich, ob der erhaltene Meßwert tatsächlich das individuelle Niveau, d.h. die dem Individuum eigentümliche Gleichgewichtslage der elektrophysikalischen Äquivalenterscheinungen der vegetativen Grundfunktionen darstellt – oder ob im Moment der Messung eine von der individuellen Ausgangslage abweichende regulatorische Zacke erfaßt wurde. Es könnte hier der grundsätzliche Einwand gebracht werden, daß die beobachteten Eltern-Kind-Korrelationen tatsächlich nur darauf zurückzuführen sind, daß die zur selben Zeit untersuchten Versuchspersonen von einem mit dem EDG korrelierten Umweltfaktor (etwa Wetter und Klima) gleichermaßen getroffen werden und damit die positive Korrelation also nicht der Ausdruck eines erblichen Zusammenhanges wäre. Gegen diese Auffassung spricht jedoch die festgestellte relative individuelle *Stabilität* des akralen EDG, die Annahme erscheint gerechtfertigt, daß die von den verschiedenen Autoren nachgewiesenen Einflüsse des Wetters auf das Körper-EDG für das akrale EDG keine so große Bedeutung haben. Die Sonderstellung der Akren (speziell der palmaren bzw. plantaren Seite) in ihrem regulativen Verhalten, mit der elektrischen Leitfähigkeit erfaßt, gegenüber der übrigen Körperoberfläche betonen *Gildemeister*, *Regelsberger*, *Richter*; eine Parallele findet sich in der geringen «Ansprechbarkeit» der Akren z.B. auf die vasodilatatorisch wirkende Nikotinsäure, während die Gefäße des Kopfes, Rumpfes und der proximalen Abschnitte der Extremitäten auf dieses Pharmakon stärker reagieren (*Hasse*, *Condorelli*, *Schulze*). Da die EDG-Reaktion auf bestimmte Wettereinflüsse bei den verschiedenen Individuen nicht gleichförmig ist (*Aichinger*), hier also konstitutionelle und wahrscheinlich erbliche (*Rudder*) Reaktionsunterschiede des Vegetativums vorliegen, wird man natürlich auch hinsichtlich des akralen EDG bei der Untersuchung von Familienverbänden erblich bedingte positive Elter-Kind-Korrelationen erwarten dürfen.

Die Erbbedingtheit und relative Umweltstabilität vegetativer Reaktionsweisen sind an den verschiedensten Funktionen nachgewiesen (*Curtius*, *Hanhart*, *Mayer-List* und *Hübener*, *Lehmann* und *Hartlaub*, *Kahler* und *Weber*, *v. Verschuer*, *Weitz* u. a.). Die auf das vegetative System wirkenden Umweltfaktoren sind vielfältiger Art, sie treffen erfahrungsgemäß die beiden Geschlechter in unterschiedlichem Ausmaß und werden von ihnen wohl auch unterschiedlich verarbeitet. Als wesentliche Umweltsfaktoren sind zu nennen: Ernährungs- und besondere Lebensgewohnheiten, psychische Insulte und Dauereinwirkungen besonderer Art, Klima und Wetter, Infektionen, Pharmaka, Genußmittel. Konstitutionelle Unterschiede

in der Reaktion auf diese Umweltwirkungen dürften hauptsächlich in unterschiedlichen Reaktionsweisen des vegetativen Systems begründet liegen. Man beobachtet immer wieder, daß der Organismus bestrebt ist, eine einmal eingespielte vegetative Grundeinstellung (die genotypisch bedingt sein kann; *Curtius* und *Korkhaus*, *v. Verschuer*) beizubehalten. Diese Grundeinstellung kann sich im individuellen Ablauf eines Lebens ändern. (Vgl. die beobachteten Altersunterschiede; in der Gravität bis Mens III Vorwiegen der parasympathischen Reaktionslage *Ratschow*.) Weitere Zusammenhänge zwischen der Hautleitfähigkeit und innersekretorischem System sind mehrfach nachgewiesen (*Brill*, *Regelsberger*).

Nach den vorstehend nur skizzierten bisherigen Ergebnissen erscheint es sicher, daß die verschiedenen Anteile des vegetativen Geschehens in sehr komplexer Weise miteinander verknüpft sind. Der Hautwiderstand gibt einen Ausschnitt aus diesem Geschehen; er ist ein komplexer quantitativer Ausdruck für die augenblickliche vegetative Gleichgewichtslage des Gefäß-Nerven-Drüsen-Systems der Akren, wobei der Kapillardurchblutung, der Schweißdrüsenfunktion und der Permeabilität der Zellmembranen eine wesentliche Bedeutung zukommen dürfte. Eine Analyse dieses Komplexes nach genetischen Radikalen erscheint vorerst nicht möglich, da die verschiedenen Anteile untereinander funktionell weitgehend korreliert sind. Vielleicht führen die neuerdings von *Drischel* entwickelten Theorien hier weiter.

Die Frage nach den genetischen Grundlagen des elektrischen Hautwiderstandes läßt sich so nur ganz allgemein beantworten. Man wird mehrere Erbfaktoren, die man wohl im allgemeinen als kleinere Allelenreihen auffassen muß, vermuten müssen. Eine besondere Rolle könnten dabei übergeordnete Gengruppen spielen, etwa im Sinne reizverstärkender Gene (*Lenz*, *v. Pfaundler*) oder Genen, die sich funktionell in der Richtung einer Stabilisierung gegenläufiger Regulationsmechanismen auswirken (stabilisierende Dämpfungsfaktoren).

Zusammenfassung.

Das akrale Elektrodermatogramm zeigt eine große Gruppenvariabilität. In der Verteilung der Meßwerte finden sich Alters-, Geschlechts- und Seitenunterschiede. Die Leitfähigkeit der Haut an den Akren für den elektrischen Gleichstrom ist individuell relativ konstant. Die Frage der Umweltwirkungen auf die Hautleitfähigkeit wird diskutiert, Beziehungen zwischen dem Elektrodermatogramm

und dem Nikotingenuß sind wahrscheinlich. In Familienuntersuchungen zeigt sich eine positive Korrelation zwischen den Meßwerten der Kinder und denen ihrer Eltern. Es wird angenommen, daß die Hautleitfähigkeit ein komplexes Merkmal ist, das sich genetisch gesehen aus mehreren Allelenreihen herleitet.

Résumé.

L'électrodermatogramme concernant les parties périphériques présente une très grande variabilité suivant les groupes différents. Les valeurs numériques des mesures comportent des différences dépendant de l'âge, du sexe et du côté où la mesure est effectuée. La conductibilité de la peau pour le courant continu est aux parties périphériques relativement constante suivant les individus. L'auteur discute la question de l'action du milieu ambiant sur la conductibilité de la peau. Il est probable qu'il existe un rapport entre l'électrodermatogramme et l'emploi de la nicotine. Les recherches effectuées dans les familles révèlent une corrélation positive entre les valeurs numériques des mesures prises sur les enfants et celles prises sur les parents. On peut supposer que la conductibilité de la peau est un caractère complexe qui, du point de vue génétique, dépend de plusieurs séries d'allèles.

Summary.

The acral electrodermatogram shows a great variability within the groups. In the distribution of the measurement figures differences are found which are due to age, sex and the side on which the measurements were made. The conductibility of the skin for the electric continuous current is individually relatively constant at the peripheral parts. The influence of the environment on the conductibility of the skin is discussed. It is probable that a connection exists between the electrodermatogram and the use of nicotine. In family investigations a positive correlation was found between the figures for the measurements made on the children and those made on their parents. It is assumed that the conductibility of the skin is a complex character which from a genetic point of view depends on several series of alleles.

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B. Lindegård: **Variations in Human Body Build. A somatometric and X-ray cephalometric investigation in Scandinavian adults.** (Acta psychiat. neurol. Suppl. 86.) Munksgaard, Copenhagen. 163 pp. Sw.Crs. 20.–.

The author of this book shares the opinion of many others that previous attempts to describe and classify human body types are in many respects unsatisfactory. One of the main difficulties, in my opinion, is that authors have tried to base a classification of something that is continuously changing (i. e. what is generally called *constitution*) on single momentary observations or measurements. The clini-

cian needs a typology of longitudinal significance, not just cross-sectional information which may become invalid as the patient grows older. It is obvious that because the individual physical and mental constitution does change with time an ideal typology remains a practical impossibility. We must therefore rest satisfied with the best possible approximation, i.e. one which takes best account of traits that are not subjected to major time changes. By limiting his study to purely descriptive aspects of body build the author has avoided all the ambiguities connected with the concept «constitution».

The author has examined 181 Swedish males, 20 years of age, and 57 Swedish conscripts, 20 years of age. In regard to the first group the data include X-ray studies of the head. To include also females, anthropometric data of 300 24-year-old Norwegian women were collected from the material published by *Schiötz*. The presentation of the primary data is very short and possible biases in the selection have not been discussed. One is left very much in doubt whether the examined individuals constitute a random sample of Scandinavian adults.

The body type is classified according to a factorial system composed of a length, sturdiness, muscle and fat factor. The main idea has been to classify each individual in regard to these four factors by his deviation from the mean expressed in sigma units. For example the length factor is determined by measuring tibia and radius length. The correlation between these two was found to satisfy the regression equation $Y = 0.39\,X + 9.6$, X being the tibia length. By inserting the actual tibia length of a particular individual for X and solving the equation an expected Y-value is obtained. The deviation of this expected Y-value from the measured radius length of the same individual, calculated in sigma units, denotes the length factor. This is just to say that each individual is classified according to his position above, below or occasionally on the regression line. However, as far as I can make out, this does not amount to much more than an excellent statistical description of the variates (i.e. individuals) of the series examined by the author; as such the description does not appear to be original.

There is, of course, no difficulty in creating a system of statistical classification, the only purpose of which is to describe accurately the variates of a specific series of observations. The difficulty lies in creating a classification which will be practically useful in describing individuals who do not belong to this specific group. For this purpose one would have to take age differences into account and secure sufficiently large and unselected series of individuals of different ages so that a specific individual when examined could be compared with his proper age specific regression line. In as much as this seems to be a useful approach to the description of body type the author's rating system would appear to be a noteworthy suggestion.

As compared to other systems of classification which are either rather subjective or take only very few anthropometric variates into account (e.g. *Strömgren*'s or *Rohrer*'s indices), the author's ratings represent much better objective descriptions. The interpretation of the biologic meaning of such descriptions, however, will be connected with the same basic difficulties as adhere to previous descriptions insofar as one tries to grasp in a cross-sectional formula something that does in fact vary with time.

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